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OCCUPATIONAL DEAFNESS

Meyer S. Fox, M.D., Milwaukee

• *A worker's hearing can be damaged temporarily or permanently by sufficiently loud occupational noise, whether explosive or continuous. Audiograms made before and during the course of employment are essential to a program of conservation of hearing; they are also essential for medicolegal purposes. Medical supervision is important. The physician who is consulted in disputes about cases of allegedly occupational deafness is on safe ground when he confines himself to statements of demonstrated fact and when he avoids suppositions. The otolaryngologist is especially qualified to collect the facts needed to conserve the hearing of workers and to prevent economic loss to employers from ill-founded claims.*

Occupational deafness is assuming increasing importance in our everyday life. Not only does it directly affect the workers and employers but also it concerns other segments of society. As physicians we are primarily interested in the medical and medicolegal aspects of the problem. As otologists we are concerned with the hearing and communication problems. Because of space limitation, it will be impossible to go into any detailed discussion. I shall therefore confine this paper to some personal recommendations and observations that I feel may be of interest and use to the practicing otolaryngologist.

Trauma

Occupational deafness as herein used denotes hearing loss in one or both ears, partial or complete, arising during the course of, or as the result of, one's employment. It may occur suddenly, as the result of traumatic injury, intense blasts, or explosions, or gradually, as the result of prolonged exposure to hazardous noise levels. Direct trauma to the ear usually results from blows, foreign objects, and burns due to sparks and molten metal. The local trauma to the area may be followed by perforation of the tympanum and infection and often is associated with a hearing loss of the conductive or mixed type. These injuries are usually unilateral and tend to heal with proper management. It has been my experience that burns of the ear canal and perforations of the tympanum due to sparks and molten metal are much more common than one would gather from current literature on the subject. Direct blows to the head can result in a hearing loss due to nerve damage, functional hearing tests revealing audiograms similar to those found in noise deafness.[1]

The term acoustic trauma is often used to include industrial noise deafness as well as the sudden hearing loss produced by loud noises such as blasts, explosions, and gunfire. Davis,[2] however, feels that the two conditions would better be described by separate terms, in order that one may logically distinguish between them. He therefore uses the term acoustic trauma to mean the immediate injury produced by one or a few exposures to intense sounds, as illustrated by the hearing loss resulting from blasts or explosions. Industrial noise deafness, on the other hand, is used to describe the loss of hearing that develops over a period of months or years of working in an environment of hazardous noise levels.

Noise

Noise has been defined as unwanted sound. It is the result of acoustic waves occurring at random frequencies and intensities. When the normal ear is exposed to noise at damaging intensity levels for a sufficiently long period of time, a temporary depression of hearing results, which disappears after a period of rest. This temporary hearing loss is called "temporary threshold shift." When the ears are exposed for longer periods or to more intense sounds, the hearing loss becomes more severe and the recovery is incomplete. That portion of hearing that never returns is referred to as noise deafness.

What are the effects of noise? We know definitely that noise can and does cause loss of hearing and that it interferes with communication. These are referred to as the auditory effects. The nonauditory effects of ordinary industrial noise are, in my opinion, vague and indefinite, the symptoms depending a great deal upon the personal motivation of the worker.

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There are many factors that affect the degree and extent of hearing impairment found in cases of noise deafness.[3] These are (1) intensity or loudness of the noise, (2) frequency spectrum of the noise, (3) period of exposure, (4) individual susceptibility, (5) age of worker, (6) coexisting ear disease, (7) character of surroundings in which noise is produced, (8) distance from source, and (9) position of each ear with respect to sound waves. The four most important of the above factors are (1) how loud the noise is (the sound-pressure level), (2) what type of noise it is (the frequency characteristics), (3) how long the period of exposure is (the duty-cycle per day and the length of total employment), and (4) how susceptible the worker is (whether he has so-called tin ears or tough ears).

The hearing loss resulting from noise deafness has certain characteristics that are of interest to the otolaryngologist. In the early stages of noise deafness the pure-tone audiogram is characterized by a sharply localized dip in the threshold curve between 3,000 and 4,000 cps. At this stage the subject is not aware of his loss and his only complaint may be due to tinnitus. As degeneration continues, the hearing for the still higher frequencies is affected and gradual involvement of the speech zone range occurs. The development of the hearing loss is slow, and frequently the worker is totally unaware of its existence and is apt to disregard it until he is quite deaf.

The hearing loss in both ears is quite similar in extent and degree, and vestibular symptoms are rarely encountered. The local otological findings are usually normal in appearance. The pathology in cases of noise deafness is involvement of the inner ear, resulting in disruption and degeneration of the hair cells of the organ of Corti with secondary degeneration of the ganglion cells. Because of the nature of the involvement of the inner ear, recruitment restrictions with respect to inability to tolerate loud sounds are usually observed. Treatment of these cases is of no avail, and, therefore, every effort should be directed toward hearing conservation.

Medicolegal Aspects of Noise Deafness

When the otolaryngologist is called upon to examine and evaluate cases involving alleged loss of hearing due to industrial noise, he is confronted with many problems. Before forming an opinion that the worker has a sustained hearing loss due to noise exposure, the otolaryngologist must be satisfied that (1) the worker has a nerve-type hearing loss characteristic of noise deafness, (2) the sound survey studies of the working areas reveal that the noises are of a type and of sufficient intensities to cause hearing loss, (3) there has been sufficient exposure time, and (4) other local and medical causes for hearing loss have been ruled out by proper history, otological examinations, and functional hearing tests.

Too often I have heard physicians describe the results of a worker's history and functional hearing tests, both of which were insufficient to permit the differential diagnosis of noise deafness. I have also heard testimony before industrial commissions on workers employed in noisy industry for many years in whom the hearing loss was attributed to high blood pressure, infection, heart disease, diabetes, or advancing age simply because the functional hearing tests disclosed a high-frequency hearing loss. The otolaryngologist is not justified in ascribing the hearing loss to such causes, completely ignoring the fact that the worker has been continuously employed at a punch press, riveting machine, or drop hammer for the past 10 or 20 years. Nor is he justified in attributing the deafness to occupational origin, when the otological examination and functional hearing tests reveal findings consistent with otosclerosis, middle ear disease, and conductive deafness.

The otolaryngologist who appears as a medical witness in these cases must be an impartial and disinterested expert who will assist the courts and commissions in resolving the medical problem at hand. He must be objective and scientific and should not concern himself with the social and economic aspects of the problem. Decisions as to when, how much, or under what condition compensation is to be paid for loss of hearing are not matters for the medical man to decide. These are the functions of the commissions and courts. His statements should be based upon reasonable medical opinions and conclusions and not upon mere speculation. What are the words that throw the testimony into the category of speculation? Some of them are "may," "could have been," "could be," "might," and "might have been." These are all terms of conjecture. As a rule, the opinions of the medical expert, when appearing before industrial commissions, need be based not upon medical certainty but rather upon medical probability. Probability applies to that which is so reasonable or well evidenced that it almost induces belief. In other words, the testimony should be based upon what the expert would ordinarily expect to find in the usual circumstances.

Some of the more thorny medicolegal questions that have arisen are as follows: 1. At what level of sound intensity and over what period of exposure does damage to hearing take place? 2. What was the status of the employee's hearing when he came to work for the employer? 3. What tests should be used for determining the hearing ability of the worker? 4. What formula should be used to evaluate these hearing tests and to express the results in terms of hearing disability? 5. Which of several hearing tests made by several otolaryngologists at various times should be used to evaluate the hearing loss? 6. Are some workers more susceptible to noise-induced hearing loss than others? 7. How are we to determine the permanency of the hearing loss if the worker continues at his employment? 8. What consideration should be given to the factor of age? 9. What consideration should be given to medical and degenerative conditions that might affect the hearing loss? There are also numerous legal questions as to the intent and interpretation of existing

compensation laws concerning noise deafness. These questions are gradually being answered by authoratative decisions of the higher courts of the various states.[4]

In reviewing the medicolegal problems, it is my opinion that the chief cause for dispute arises from the fact that there were no reliable records that could be used as a base line to determine the worker's hearing at the beginning of employment and during the course of employment. Another important controversial medicolegal development is that pertaining to the various methods for determining hearing loss and for converting this hearing loss in terms of percentage of hearing disability. That there are differences of opinions is established by the fact that various states have different approaches to the same problem. The American Medical Association and the American Academy of Ophthalmology and Otolaryngology recognized the inadequacy of the existing methods of determining hearing disability and a committee of eight persons was appointed to study the problem. After several years of study, this committee published a report on principles for evaluating hearing disability.[5] All otolaryngologists interested in the problem of industrial noise deafness are urged to study this report.

Hearing Conservation Programs

The otolaryngologist, by virtue of his special training, interest, and daily clinical experience with hearing problems, has the qualifications that enable him to be a consultant in the planning and management of industrial hearing conservation programs. In a previous publication [6] I pointed out that the three major objectives of such a problem are to (1) conserve the hearing of workers, (2) avoid unnecessary economic loss to employers, and (3) collect the facts and data in order to facilitate the accomplishment of the two foregoing objectives.

The first requisite of an effective hearing conservation program is a thorough sound survey of the working areas. Such a study is necessary to scientifically determine the frequency characteristics and intensity levels of the noise present in these areas. The information thus gained should indicate whether excessive noise levels are present and, if so, the amount and type of acoustical treatment and individual ear protection that might be required in such working areas. The next step is to obtain a suitable room for the performance of hearing tests. The testing room should be situated in an area that will permit the satisfactory performance of hearing tests without interference due to extraneous noises. In some cases acoustical treatment of existing rooms will result in a satisfactory reduction of the extraneous noises. In other situations acoustical treatment will not bring about the desired result. Where this is not feasible, prefabricated acoustical booths now commercially available provide a satisfactory place for the auditory tests. The personnel who are to do the testing should be sufficiently trained and supervised by the otolaryngologist so that they will develop skill and interest in this work. For the ordinary industrial hearing conservation program, only pure-tone air-conduction audiograms need be taken, and these can be made with a simple, portable, properly calibrated audiometer.

The next phase of the hearing conservation program is the installation of preplacement pure-tone audiometric tests of the workers. This is a must. The preplacement pure-tone audiogram is a base line from which all subsequent studies concerning the worker's hearing status are made. The records that are used should show the audiometric and otological findings and pertinent items of medical and industrial history. All workers exposed to high-intensity noise levels should have periodic checkups of their hearing.

The results of all hearing tests are reviewed and evaluated, and those workers who show significant hearing loss at the beginning of employment or during the course of employment are referred to the otologist for examination and further hearing studies. This procedure results in the establishment of accurate records that can be used for purposes of jobplacement and of ear protection and as a base line for future audiometric studies. It also establishes valid records made by a qualified otologist that can be used in the event industrial claims of hearing loss arise at a later date. I am aware of the fact that many industries have purchased audiometers and have turned over the job of testing workers' hearing to health and safety personnel without adequate medical supervision. The records that are made are filed away for use in the event of future compensation claims. It is unnecessary for me to point out that this is not practicing good medicine.

It goes without saying that the ideal hearing conservation program would entail the removal of the noise at its source. The extent to which these measures can be expected to decrease noise levels varies with the machines, the operations, and the physical plant and is a matter better left to the acoustical and industrial engineers. In the areas where noise levels cannot be effectively reduced by means presently available, the hearing of workers can be protected by the use of ear plugs. Considering that any protective device to be inserted into the ear canal is essentially a foreign body, it becomes obvious that the supervision of this aspect of the hearing conservation program should be in the hands of medical personnel and that all necessary hygienic measures should be taken. It has been my experience that the big problem is gaining the acceptance and cooperation of the workers and of convincing them it is not a sign of weakness but only good sense to protect their hearing with ear protectors.

Summary and Conclusions

Occupational deafness is defined as hearing loss occurring during the course of, or as the result of, one's employment. The hearing loss may occur suddenly, as the result of direct traumatic injury or of explosions, blasts, or gunfire, or it may occur gradually, as the result of prolonged exposure to hazardous

noise levels. As otolaryngologists, our interest and function is to conserve and protect human hearing. Therefore, it behooves us to meet the challenges of occupational deafness by active interest and participation in the various aspects of the problem.

208 E. Wisconsin Ave.

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ANESTHETIC MANAGEMENT OF PATIENTS WITH RESPIRATORY DISEASE

Nicholas M. Greene, M.D., New Haven, Conn.

• *Respiratory disease in a surgical patient can represent a serious complication to the giving of anesthesia. Preoperative management must include correction of the underlying pulmonary pathology, where possible. For preanesthetic medication, the barbiturates are preferable to analgesics. While the anesthetic agent itself cannot be related to any adverse effects on preexisting pulmonary infections nor, alone, have influence on postoperative respiratory complications, it must still be admitted no presently available agent or technique is ideal. The selected procedure must therefore be considered in the light of its particular advantages (e. g., bronchodilating qualities, rapid postoperative response) over predicted disadvantages (e. g., anoxia, respiratory depression). Competent postoperative supervision, preventing interference with adequate respiration, completes the program of providing safe anesthesia for patients with respiratory disease.*

One of the most frequently encountered problems in clinical anesthesia is that of the patient with respiratory disease. This problem deserves our careful attention. Unless it is successfully solved, the patient is subjected to an increased operative and postoperative morbidity and mortality, or surgery is so limited that the indicated procedure cannot be accomplished. Recent advances have been made that offer help in dealing with these patients. Although much yet remains to be learned, it is appropriate to consider some of the clinical ramifications of developments and, by combining them with older and well-recognized principles, to formulate a modern approach to this ancient problem. To limit an otherwise vast and complicated field, emphasis will be placed on those patients in whom the respiratory disease represents an incidental, albeit serious, complication to extrathoracic surgery.

Preoperative Management

Unless patients with respiratory disease are properly prepared prior to surgery, their anesthetic management during surgery will always be less than satisfactory. Preparation consists of correcting underlying pulmonary pathology insofar as possible and of eliminating factors that may increase the possibility of postoperative respiratory complications. Extrapulmonary causes of decreased ventilation must be sought out, for they are often reversible. Pleural or ascitic fluid should be removed by paracentesis, and obesity must be eliminated by an enforced program of weight reduction.

Respiratory infections must be controlled. In the upper respiratory tract, control includes treatment of chronic sinusitis and avoidance of elective surgery during acute infections, such as the common cold. In infections of the lower part of the respiratory tract, antibiotics should be administered parenterally and by inhalation of nebulized solutions if necessary. Adequate drainage of purulent secretions from bronchiectasis or lung abscesses must be assured by the use of pulmonary detergents, postural drainage, and bronchoscopic aspiration when such treatment is indicated. Patients with bronchiectasis should be operated on only after they have been able to spend several hours in the morning coughing and raising their own secretions. Actual or potential obstruction of the respiratory passages must be corrected. Patients with asthma should be desensitized to the offending allergen if possible and treated, if necessary, with cortisone and bronchodilating drugs.

Severe emphysema represents a serious and increasingly frequent complication. Because alveolar ventilation is inadequate to remove carbon dioxide, patients with emphysema have varying degrees of respiratory acidosis. Pulmonary infection may be superimposed. There may also be increased resistance to blood flow through the lungs, resulting in cor pulmonale with right-sided heart failure. Preoperatively, any myocardial decompensation is an indication for digitalization in these patients. Any infection is an indication for antibiotic therapy.

A potent carbonic anhydrase inhibitor, acetazolamide (Diamox), may be used preoperatively to decrease the respiratory acidosis. By interfering with normal renal electrolyte excretion, acetazolamide produces a bicarbonate diuresis. The resultant fall in plasma bicarbonate level is associated with a decrease in plasma pH and a lowering of abnormally high car-

From Grace-New Haven Community Hospital and Yale University School of Medicine.

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bon dioxide tensions. The exact mechanism by which acetazolamide improves alveolar ventilation remains incompletely defined, but the reduction in carbon dioxide tension may mount to 10 to 15 mm. Hg.[1] Although the beneficial effects of prophylactic administration of acetazolamide remain to be quantitated, its use in patients with severe emphysema who can be offered little else appears justified. It is especially appropriate in emphysematous patients about to undergo major upper abdominal surgery, for these are the patients whose respiratory exchange is most altered postoperatively. Acetazolamide, 250 to 750 mg. per day, may be given in one dose or two divided doses for four or five days preoperatively. It should be replaced by ammonium chloride on the day before surgery, so that the metabolic acidosis created by the acetazolamide may be lessened on the day of surgery.

Preanesthetic Medication.—Appropriate preanesthetic medication is of fundamental importance in the safe anesthetic management of patients with respiratory disease. Parasympatholytic drugs should be used in amounts somewhat in excess of the normal to reduce otherwise copious and troublesome secretions. Preanesthetic sedation should be obtained with drugs that not only produce a sense of mental relaxation and detachment but also do so without impairing ventilation. In carefully controlled studies, Lasagna and others [2] have shown that narcotics are far less satisfactory and predictable producers of euphoria than are barbiturates. For this reason alone barbiturates are preferable to analgesics for preanesthetic medication.

Also, Eckenhoff and others [3] have demonstrated that all commonly used analgesics depress respiration when given in therapeutic amounts to normal patients. Depression occurs to the extent that carbon dioxide tensions are invariably elevated, but it does not occur after hypnotic doses of barbiturates. In patients already suffering from an inability to excrete carbon dioxide normally, the use of analgesics for premedication is ill-advised unless the patient has pain. Preexisting respiratory inadequacy will not only be accentuated by analgesics but also the desired sedation will not be as predictably attained as with the use of barbiturates.

Management During Anesthesia

Choice of Anesthetic Agent and Technique.—Before consideration is given to the pharmacological and physiological properties of anesthetics as they affect patients with respiratory disease, three rather negative but nonetheless fundamental principles should be emphasized. The first principle is that none of the presently available anesthetic agents or techniques is ideal. They all have their advantages as well as their disadvantages. For patients with respiratory disease, the most satisfactory agent will be the one that provides advantages outweighing disadvantages, so that the over-all risk to the patient, although of necessity not eliminated, is diminished.

Secondly, anesthetic agents per se have no influence on the incidence of postoperative respiratory complications. For example, inguinal herniorrhaphies performed with the patient under spinal or local anesthesia are followed by respiratory complications with the same frequency as those performed with the patient under ether anesthesia.[4] Site of surgery, age, sex, body build, and, as Dripps and Deming [5] so aptly demonstrated, the care and ability with which the anesthesia is administered are all factors that do influence the development of postoperative respiratory complications. The anesthetic itself does not. Thirdly, although preexisting pulmonary infections (e. g., tuberculosis) are adversely affected by anesthesia and surgery, the degree to which they are influenced is not related to the particular general anesthetic agent used.[6] The pharmacological and physiological effects of anesthetics on the respiratory system can be discussed only with these three basic concepts in mind. They are prerequisite to an objective and scientific approach to the problem.

Use of Ether: Ether, the most potent inhalation anesthetic commonly used today, can be administered with a concentration of oxygen higher than can be used with any other agent. Surgical anesthesia with muscular relaxation is maintained with 4% ether and 96% oxygen in the inspired air. This high concentration of oxygen may prove advantageous in certain patients with severe pulmonary disease. Ether is also the only general anesthetic that, when given in concentrations adequate for moderate or light planes of surgical anesthesia, does not invariably cause depression of respiration to the point where respiratory acidosis supervenes.[7] Alveolar ventilation may actually be increased by ether, except in the deeper planes of anesthesia.

Respiratory acidosis can and most certainly does occur during the administration of ether, but it is neither as frequent nor as severe as that present with equal depths of anesthesia obtained with other agents. In patients with respiratory disease, this is a significant advantage. When and if respiratory acidosis does occur under light ether anesthesia, its presence may be, and usually is, clinically detected by alterations in the respiratory pattern. The sensitivity of the respiratory center to elevations in carbon dioxide level is depressed by higher concentrations of ether,[8] but during light anesthesia this depression is not severe enough to prevent completely the hyperventilation of respiratory acidosis. Simple and reliable objective methods of rapidly determining alveolar carbon dioxide tensions under clinical conditions are not available. The ability to recognize clinically and so to treat respiratory acidosis during moderate or light ether anesthesia is an invaluable aid in managing patients with respiratory disease.

The major disadvantage of ether as a general anesthetic in patients with respiratory disease is that recovery may be prolonged. Prolonged recovery occurs most frequently after long operations, in patients with emphysema, and after the administration of ether by the inexperienced. Recovery from ether anesthesia is not, however, accompanied by the same respiratory depression that follows recovery from equal depths of anesthesia produced by other general anesthetic agents. During the period of recovery from ether anesthesia there may be an increased production of mucus, but, as already indicated, this does not add to the

frequency of postoperative respiratory complications if adequate suctioning of the respiratory tract is carried out. Ether is not contraindicated as a general anesthetic in the presence of respiratory disease. It has, in fact, certain patent advantages. In asthma, ether is preferable to all other general anesthetic agents. With the single exception of tribromoethanol (Avertin), it is the only agent possessing bronchodilator properties.

Cyclopropane as an Anesthetic: Cyclopropane is also administered with high concentrations of oxygen. Given in anesthetic concentrations, it produces, unlike ether, depression of the respiratory center. Patients breathing spontaneously under cyclopropane anesthesia will always have respiratory acidosis. Although this depression of the respiratory center represents a disadvantage of cyclopropane, it is one for which hyperventilation artificially performed by the anesthetist can compensate. All patients, and especially those with respiratory disease, must have their respirations assisted or controlled during cyclopropane anesthesia. When respiratory assistance is given, respiratory acidosis does not supervene. That depression of respiration is not a matter of academic interest alone is attested to by the severe and dangerous falls in arterial pressure immediately after anesthesia in patients who have had acidosis. Unfortunately there are no reliable clinical signs of respiratory acidosis during cyclopropane anesthesia. Arterial hypertension associated with the acidosis may occur," but hypertension may also exist in its absence.[10]

The greatest advantage of cyclopropane in patients with respiratory disease lies in the ready reversibility of the anesthesia induced. If the anesthetic is properly administered, the patient will react immediately postoperatively with minimal residual respiratory depression. Because of its reversibility, in capable hands cyclopropane has proved eminently satisfactory in the anesthetic management of patients with respiratory disease, although the drug should not be administered to patients with asthma because of the possibility of initiating bronchospasm.

Anesthesia with Intravenously Given Barbiturates: Anesthesia induced with intravenously given barbiturates is associated with respiratory depression in much the same way as is cyclopropane anesthesia. The respiratory center becomes so insensitive to alterations in carbon dioxide tensions during barbiturate anesthesia that respirations are maintained chiefly by the chemoreceptors of the aortic and carotid bodies. These receptors respond to changes in oxygen saturation, not to changes in carbon dioxide. Again, as with cyclopropane, there are no reliable clinical signs during barbiturate anesthesia to indicate when depression has progressed to respiratory acidosis. The anesthetist must appreciate this lack of clinical signs and correct hypoventilation by artificial means.

Unlike the effects of cyclopropane, those of the so-called short-acting barbiturates extend well into the postoperative period, causing a subtle and perhaps clinically unrecognizable respiratory depression. Because the action of intravenously given anesthetics is not readily and rapidly reversible,[11] depending as it does on inactivation by metabolic processes, these agents are often not the most desirable ones for use in patients with respiratory disease. In the presence of real or imminent obstruction to the respiratory tract, they are contraindicated.

Intravenously given anesthetics are usually used in conjunction with relatively weak inhalation anesthetic agents such as nitrous oxide. Fink has recently emphasized[12] that, after discontinuation of administration of nitrous oxide, there is a temporary but significant drop in alveolar oxygen concentration as the nitrous oxide diffuses out of the blood into the alveoli. The resultant anoxia may be evidenced by cyanosis even in normal patients. In patients with respiratory disease, this type of anoxia must be guarded against, because it will be more profound and more prolonged.

Use of Muscle Relaxant Drugs: Muscle relaxant drugs have much to recommend them in patients with respiratory disease, but their use is associated with two distinct dangers. The first is that, when muscle relaxants are given in therapeutic doses, the muscles of respiration are impaired. This condition implies that such drugs can be used safely only when the anesthetist is willing and able to provide adequate respiratory exchange at all times. The second danger is that the duration of action of these agents may extend into the postoperative period. This possibility has been lessened but not eliminated by the introduction of succinylcholine chloride, with its short duration of action. Prolonged apnea can and does occur after the use of succinylcholine chloride. It may occasionally be due to abnormally low plasma levels of cholinesterase, the enzyme responsible for the metabolic degradation of succinylcholine. More frequently, prolonged apnea is probably due to overventilation, resulting in abnormally low carbon dioxide levels or in depression of the Hering-Breuer reflex.[13] Longer acting muscle relaxants such as tubocurarine chloride or laudexium (Laudolissin) methylsulfate are even more apt to cause postoperative respiratory impairment, even though at subclinical levels.

Use of Conduction Anesthesia: Conduction anesthesia, by providing ideal operating conditions with minimal disturbance of respiratory function, frequently represents the anesthetic method of choice in treating respiratory cripples. It also has limitations and dangers that under certain circumstances make its use in such patients highly inadvisable. Whether conduction anesthesia will prove the anesthetic method of choice in a given patient depends upon three factors. The first is the magnitude of the surgery. Minor surgery is always best performed with use of local anesthesia in patients with respiratory disease. Local anesthesia is not necessarily the best for use in major surgery. Whether local or, indeed, any type of conduction anesthesia is indicated for major surgery will depend on the second factor, the site of surgery. Conduction anesthesia is eminently satisfactory for patients with respiratory disease during major surgery performed below the umbilicus. Spinal, epidural, or nerve-block anesthesia may then be used as indicated.

The advantages of spinal and epidural anesthesia, however, are offset in such patients if the sensory block must be carried high enough to permit surgery on the upper part of the abdomen. The effects of high and low spinal anesthesia cannot be compared. In poor risk cases, low spinal anesthesia is indicated because profound anesthesia can be obtained with little derangement in normal physiology. However, high spinal anesthesia is contraindicated in such patients because it is achieved only at the expense of profound alterations in cardiac output; peripheral blood flow; and hepatic, renal, and cerebral circulation. In respiratory cripples, respiratory efficiency is also diminished. Administered under modern anesthetic techniques, general anesthesia can provide the same operating conditions in the upper abdomen as can spinal anesthesia, without producing the same physiological changes.

The third and final factor that will determine whether conduction anesthesia is the method of choice is the skill and experience of the person administering the anesthesia. This point is well illustrated by considering the use of brachial block anesthesia for surgery on the upper extremities and local anesthesia for abdominal surgery. While brachial block is the logical choice for procedures on the upper extremities in a patient with respiratory disease, an inadvertent pneumothorax during the anesthesia might prove disastrous. Such an anesthetic procedure is indicated only if it is safely and efficiently performed by one highly skilled and trained in the method. The novice should avoid such a technique under these conditions.

The same principle applies to the administration of local anesthesia for abdominal surgery. Major intra-abdominal operations can be safely and efficiently performed with the patient under local anesthesia. Any theoretical advantage of local anesthesia is immediately negated, however, if the patient experiences pain, if poor operating conditions result, or if futile attempts are made to compensate for inadequate local anesthesia by the administration of analgesics and sedatives. The use of analgesics and sedatives is especially unfortunate. Such centrally acting drugs never wholly obtund surgical pain, but they do depress respiration. If general anesthesia must be instituted to allow surgery to continue, it must be given under difficult circumstances to an agitated, severely depressed patient, who was a poor risk to start with. Local anesthesia for abdominal surgery must be administered only by those with experience, by those with full understanding of the neuroanatomy involved, and by those patient and gentle by nature. As modern anesthesiology has developed, such persons have become progressively more rare.

Management of Ventilation.—It is apparent from the preceding discussion that one of the keys to the safe anesthetic management of patients with respiratory disease lies in maintenance of adequate respiratory exchange. Adequate respiratory exchange means not only providing an airway that is completely patent at all times but also assuring an alveolar ventilation adequate to provide normal oxygen uptake and carbon dioxide excretion. Normal arterial oxygenation is relatively easily obtained in modern anesthesia; normal carbon dioxide excretion is not. The vast majority of modern anesthetic techniques either depress the respiratory center or impair the normal function of the respiratory muscles, or both. The end-result is depression of alveolar ventilation to the point that, although oxygenation is normal, carbon dioxide accumulation takes place.[7]

When carbon dioxide accumulation occurs, it becomes the responsibility of the anesthetist to augment alveolar ventilation by artificial means. As already indicated, the clinical detection of hypoventilation is difficult if not at times impossible. Respiratory rate and motion of the rebreathing bag or of the patient's chest are notoriously unreliable indexes of alveolar ventilation. A 10% reduction in alveolar ventilation results in respiratory acidosis but is clinically undetectable by even the most experienced observer. Cyanosis is no guide, for it may be absent when severe acidosis is present. Cardiovascular responses such as hypertension and tachycardia are altered by the anesthetic agent itself. In view of the difficulty of detecting subtle yet serious respiratory inadequacies during anesthesia even in normal patients, together with the frequency with which they occur, it should be assumed that all patients with respiratory disease should have their respirations assisted or controlled during general anesthesia. Whether respirations are assisted or controlled depends mainly upon the degree of artificial ventilation required.

The most satisfactory method to be employed to assist or control respirations during anesthesia has not yet been defined. There are two general methods. One consists of manual compression of the anesthesia breathing bag and the other of using one of several currently available mechanical respirators. Properly employed, each method will accomplish the desired objective of increasing alveolar ventilation. Intermittent positive pressure applied to the rebreathing bag can aid alveolar ventilation as well as most mechanical devices designed for the same purpose. Manual methods have the disadvantage of being satisfactory only when employed by meticulous, physiologically oriented anesthetists who are willing and able to concentrate on the adequacy of every respiration. While a few deep breaths may correct hypoxia, a fourfold increase in alveolar ventilation lasting six minutes is required to reduce a carbon dioxide tension of 100 mm. Hg back to a normal of 40 mm. Hg.[7] Most respirators will aerate the alveoli of an anesthetized patient more efficiently than a preoccupied or indolent anesthetist.

The chief disadvantages of mechanical respirators, aside from their expense, arise from two sources. One is that no matter how well tooled they are, mechanical failure is always a possibility. Such an event, usually occurring at a most inappropriate time, can be disastrous if not recognized immediately. The other disadvantage is that personal contact with patients is lost when machines are used. Such loss of personal contact

is a matter for serious consideration in this day of increasingly complex anesthetic techniques. Since both methods are, however, satisfactory when correctly employed, the decision of which to use will usually depend upon the philosophy and training of the anesthetist and the financial resources of the hospital. From a practical point of view, at the present time it is more important to spend time, effort, and energy emphasizing the necessity of adequate ventilation and how it may be manually attained rather than to change anesthetists into mechanics versed in the mechanical problems and idiosyncrasies of various pumps, valves, and flywheels. It is economically certainly more feasible. The ultimate welfare of the patient will also be increased.

There is only one situation in which use of certain types of mechanical respirators has distinct advantages over manually performed ventilation. That situation occurs in patients with decreased cardiac output. During inspiration there normally exists a negative intrathoracic pressure that aids in venous filling of the right side of the heart. This pressure is eliminated by methods of artificial ventilation devoid of any negative phase and consisting solely of intermittent positive pressure. Patients whose cardiovascular status is precarious may react adversely to such positive pressures by showing further falls in cardiac output and blood pressure.[14] Since manual control of respiration eliminates negative pressures throughout the respiratory cycle, a mechanical ventilator providing negative pressure during expiration should be employed in such patients.

Postoperative Management

Immediate Postoperative Period.—The immediate postoperative period is as critical for a patient with respiratory disease as the operative period. The importance of competent supervision in a postanesthetic recovery room staffed by specially trained personnel cannot be overemphasized. Attention is centered on the prevention or correction of any interference with adequate respiration. Depression of the respiratory center caused by analgesics given during surgery is to be counteracted by use of specific antagonists such as nalorphine hydrochloride or levallorphan (*p*-3-hydroxy-N-allylmorhinan) tartrate. If caused by barbiturates or inhalation anesthetics, respiratory depression must be compensated for by artificial ventilation until such time as the respiratory center regains its normal threshold.

Any inefficiency of the muscles of respiration due to muscle relaxants must similarly be compensated for by artificial respiration. Muscle relaxant antagonists such as edrophonium (Tensilon) chloride are not to be wholly relied upon, for, although they may be temporarily effective, their effects may wear off before normal muscle activity returns. The fundamental danger of respiratory obstruction caused by soft tissues, secretions, or vomitus must be constantly guarded against. Obstruction is still one of the foremost preventable causes of death in the immediate postoperative period. Administration of oxygen should be employed unhesitatingly. Carbon dioxide inhalation is unnecessary in the immediate postoperative period. Excessive carbon dioxide levels are often already present, especially in the patient with respiratory disease. Addition of further carbon dioxide may make matters worse.

Management in the Ward.—After the immediate postoperative period has passed and the patient has returned to the ward, the respiratory cripple still has many dangers to overcome. Prophylactic administration of antibiotics is often indicated in these patients. Repeated, thorough physical examinations of the chest should be performed, including x-rays when necessary. Patchy areas of atelectasis should be treated by forced coughing and hyperventilation, by frequent changes of position and by early ambulation. Larger areas of atelectasis are an indication for immediate bronchoscopy. Because of their action as respiratory depressants, analgesics should be used sparingly and only for the relief of pain, not as sedatives. After certain types of surgery, nerve blocks may be effective in relieving pain, thus avoiding the use of analgesics. If such blocks are utilized, they must be performed at frequent intervals with relatively short-acting local anesthetics of known safety. At the present time no safe local anesthetics are available that will provide anesthesia for more than a matter of hours.

The performance of a tracheotomy at the conclusion of surgery may add greatly to the safe postoperative recovery of selected patients with pulmonary disease. When the patient is unable to raise his own secretions either because they are so profuse or because he is so weak, a prophylactic tracheotomy may prove lifesaving. This procedure will also decrease respiratory dead space by as much as one-third or even one-half of its normal 150 cc. Reducing dead space by 50 cc. in an emphysematous patient with a fixed tidal volume of 300 cc. will increase the amount of inspired air available for alveolar ventilation by about 30%. As important as the decision to do a tracheotomy, however, is the quality of care devoted to the tracheotomy after it has been performed. Suction through a tracheotomy must be done aseptically, gently, and rapidly. If suction is not correctly performed, hypoxia ensues, tissues are traumatized, and secretions increased.[15] Special equipment is necessary to deliver high concentrations of humidified oxygen to a tracheotomy. Insertion of a nasal catheter through the tracheotomy tube is to be condemned. Routine tracheotomy care is not to be delegated to the routinely trained. It requires special instruction and meticulous attention.

Summary

Safe anesthesia for patients with respiratory disease depends upon careful evaluation of each individual case. The management will vary according to the type and severity of the pulmonary pathology, the site and nature of the proposed surgery, the pharmacological effects of the anesthetic agent, and the skill of the person administering the anesthetic.

789 Howard Ave. (4).

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IMMUNIZATION OF INFANTS WITH LIVING ATTENUATED POLIOMYELITIS VIRUS

LABORATORY INVESTIGATIONS OF ALIMENTARY INFECTION AND ANTIBODY RESPONSE IN INFANTS UNDER SIX MONTHS OF AGE WITH CONGENITALLY ACQUIRED ANTIBODIES

Hilary Koprowski, M.D., Thomas W. Norton, Pearl River, N. Y., Klaus Hummeler, M.D. Joseph Stokes Jr., M.D., Philadelphia, Andrew D. Hunt Jr., Flemington, N. J., Agnes Flack, M.D., Clinton, N. J. and George A. Jervis, M.D., Thiells, N. Y.

• Two types of living attenuated poliomyelitis virus were administered by mouth to 24 bottle-fed infants by adding the virus preparations to the formula. Sixteen received the SM strain (representing type 1), two received the TN strain (type 2), and six received both strains at different times. Ingestion of SM was followed promptly by an asymptomatic alimentary infection, demonstrated by isolating the virus from the feces. Repeated doses were necessary to establish the carrier state in three of these infants. Ingestion of TN by two infants was followed similarly by the isolation of type 2 virus from the feces. All infants developed active immunity after the inapparent alimentary infection. It was found safe to administer the virus to infants less than a month old. Two infants who had not received the virus were placed in cribs between those of other infants carrying SM but did not contract the infection. The presence of homotypic antibodies congenitally acquired from the mother did not prevent an active response in infants who received an adequate amount of virus.

In the course of studies conducted during the past six years, approximately 500 individuals have received by the oral route the SM (type 1) and TN (type 2) attenuated strains of poliomyelitis virus. The largest group of recipients comprised children from 3 to 12 years of age who had no demonstrable antibodies to the type of virus being administered. In one instance, the TN strain was given to a 3-month-old baby who showed the presence of type 2 antibodies probably acquired from her mother. (No blood sample was obtained from this mother for antibody determinations.) This infant became an intestinal carrier after the oral administration of the virus and developed a high titer of neutralizing antibodies 28 days after the feeding of virus.[1] Thus, here was an example that congenital passive immunity did not interfere with multiplication of the virus in the alimentary tract or with the subsequent development of active immunity. Further studies undertaken along similar lines indicated that immune serum globulin (human) administered simultaneously with the attenuated viruses (types 1 and 2) did not prevent intestinal carriage of virus or have any deleterious effect on the antibody response.[2] These findings led to the present trial with infants under 6 months of age, most of whom had circulating antibodies derived from their mothers against the type of virus being fed. Clinical data have been presented elsewhere.[3]

From the Viral and Rickettsial Section, Research Division, Lederle Laboratories, American Cyanamid Company (Dr. Koprowski and Mr. Norton); School of Medicine, University of Pennsylvania, and Children's Hospital (Drs. Hummeler and Stokes); Hunterdon County Medical Center (Dr. Hunt); Medical Department, Clinton Farms (Dr. Flack); and Research Department, New York State Department of Mental Hygiene, Letchworth Village (Dr. Jervis).

Material and Methods

Strains of Virus.—The history and properties of the TN (type 2) and SM (type 1) strains have been described fully in extensive reports published elsewhere [3] and will not be repeated here.

Administration of Virus.—SM virus-infected tissue culture fluid, either undiluted or as a 1:100 dilution in saline solution, was mixed in equal parts with glycerin. The TN virus, in the form of a 20% suspension of mouse brain and cord, was also mixed with glycerin

in equal proportions. Both preparations were stored in a dropper bottle at 4 C. Thirty drops of the TN or 3 to 9 drops of the SM preparation were measured into 4 ml. of formula. The concentration of virus in the mixture was determined in T. C. $D._{50}$ (tissue culture doses) of SM or in P. $D._{50}$ (mouse paralytic doses) of TN.[2] The infants were all bottle-fed and were given the virus-formula mixture just before a regular feeding.

Choice of Infants.—After parental consent was obtained for the studies, neutralization tests were run on serum samples from both the infants and the mothers to determine the presence of antibodies against types 1, 2, and 3 poliomyelitis virus. Tests were usually performed on a sample of cord blood obtained at birth, at which time blood was also secured from the mother. In some cases, the infant's antibodies were measured again just before virus ingestion. Infants with antibodies against either type 1 or type 2 were fed the homotypic virus, but an attempt was made to have as large a group as possible receive type 1 virus. On occasion, infants who had antibodies against both types were fed the two viruses (see below).

After the administration of virus, infants were isolated in a small wing of the hospital and access to this area was restricted to required personnel. Everything taken from the contaminated areas was disinfected either by autoclaving or by chemical means. No special precautions were taken by the nurses to avoid contact between cribs. Each infant was examined by a pediatrician before receiving virus and was under continuous medical supervision.

Laboratory Studies.—The technique used in isolating virus from stools has been previously described.[2] The pH color test [4] was employed for the determination of neutralizing antibodies in blood drawn before and after the administration of virus.

Results

Administration of Type 1 Virus.—Ten infants 1 to 4 months old comprised the first group fed the SM virus. From eight of these, as indicated in table 1 (the exceptions were infants no. 13 and 5), two blood samples were secured, the first at the time of withdrawing blood from the mother and the second just before virus feeding. As is apparent from the data in table 1, the serums of infants in general had the same type of antibodies as the serums of their mothers, but the concentrations were usually slightly lower. During the interval between the first and second bleeding, a small decrease in antibody titer was sometimes observed. The increase in antibody titers against type 2 in the blood of infants no. 2 and 4 before the administration of type 1 virus may be a reflection of experimental error in the neutralization test rather than an actual rise.

The administration of the SM strain to infant no. 15 was his second feeding with a virus. At the age of 73 days, he had been fed the TN virus (table 7) and

TABLE 1.—*Administration of Type 1 (SM) Virus to Infants at the Age of One to Four Months*

Infant No.	Antibodies Before Virus Administration: Mother Type 1	Mother Type 2	Infant Age, Days	Infant Type 1	Infant Type 2	Infant Type 3	Virus Administration: Infant's Age, Days	Amount T.C.$D._{50}$*	Alimentary Infection, Days	Antibodies After Virus Administration: Days After Virus	Type 1	Type 2	Type 3
15†	1: 4	1: 178	At birth	<1: 2	1: 91	1: 16				42	1: 362		
			119	<1: 2	1:1,024		119	4.1	3-70	71	1:1,449	1:1,024	1: 4
7	1: 64	<1: 2	24	1: 16	<1: 2	1: 44				27	1: 178		
			87	1: 8			87	5.1	1-74	44	1:1,024	1: 4	1:16
2	1: 712	1:1,024	58	1: 64	1: 64					66	1: 712	1: 23	
			84	1: 64	1: 91	<1: 8	84	4.7	1-56	84	1:1,024		<1: 8
4	1: 41	1: 64	50	1: 64	1: 64	<1: 2				50	1: 362	1: 64	
			83	1: 44	1: 178		83	3.5	3-62	77	1:1,024		
10	1: 64	1: 23	22	1: 64	1: 16	1: 16				42	1: 256		
			69	1: 16			69	2.9	1-70	71	1: 712	1: 6	<1: 2
3	1: 362	1:1,024	34	1: 64	1: 64	1: 64				50	1: 712	1: 16	
			67	1: 64	1: 64		67	5.1	3-55	77	1:1,024		1: 6
13	1: 44	1: 16	51	1: 16	1: 16	<1: 2	51	5.1	1-99	44	1: 256	1: 6	
5	1: 64	1: 64	49	1: 23	1: 256	1: 16	49	3.7	3-80	27	1: 256		
										77	1:1,024	1: 23	1: 4
8	1:1,024	1: 91	At birth	1:712	1: 32	1:178				27	1: 362	1: 16	1:16
			42	1:362	1: 16		42	2.9	1-74	55	1:1,024	1: 16	<1: 8
1	1: 11	1: 16	9	1: 4	1: 16					34	1: 64		
			35	1: 4	1: 16	1: 16	35	3.5	1-108	87	1: 362	<1: 8	<1: 8

* T.C.$D._{50}$=tissue culture $doses_{50}$, expressed as logs to the base of 10.
† Administration of type 2 virus preceded type 1 (see table 7).

TABLE 2.—*Administration of Type 1 (SM) Virus to Infants at the Age of 86 to 175 Days*

Infant No.	Antibodies Before Virus Administration: Mother Type 1	Mother Type 2	Infant Age, Days	Infant Type 1	Infant Type 2	Infant Type 3	Virus Administration: Infant's Age, Days	Amount T.C.$D._{50}$*	Alimentary Infection, Days	Antibodies After Virus Administration: Days After Virus	Type 1	Type 2	Type 3
14†	1: 6	1:256	17	<1: 8	1: 256	1:256	175	4.8	2-55	9	1:256		1:16
			147	<1: 2	1: 16					31	1:362	1:11	
16	1:178	<1: 2	At birth	1:256	<1: 2	1: 64	117	4.8	2-58	9	1: 23	1: 4	1: 4
			88	1: 16	<1: 2					31	1:256	1:16	1: 4
18	NT‡	NT	11	1:256	1:1,024	1: 64	86	5.5	2-72, 83-89	37	1:178	1:256	1: 4
			86	1: 23	1: 256								

* T.C.$D._{50}$=tissue culture $doses_{50}$, expressed as logs to the base of 10.
† Fed type 2 (TN) virus at the age of 115 days (see table 7).
‡ NT=not tested.

had responded with a high titer of type 2 antibodies. Although a very low level of type 1 antibodies was observed in the maternal blood (table 1), no antibodies were detected in the infant's serum, either at birth or at the age of 119 days, when he received $10^{4.1}$ T. C. $D._{50}$ of SM virus. This feeding was followed promptly by alimentary infection with type 1 virus lasting from the 3rd to the 70th days and by a marked rise in type 1 antibodies, as determined on the 42nd and 71st days after virus administration. There was no change in the already high level of antibodies against type 2 virus, but there was a decline in the level of type 3 antibodies.

The other nine infants (table 1) had not previously been fed virus, and the amount of SM virus they in-

The mother of infant no. 14 had a low (1:8) titer of type 1 antibodies, and at the time her baby was fed type 1 virus its serum antibody titer was <1:2. The same infant had previously received type 2 (TN) virus (see table 7), but the type 2 antibody concentration in his blood was rather low (1:16). Nine days after ingestion of SM virus, the type 1 antibody titer had risen to 1:256, and it was slightly higher 31 days after virus feeding. The unusually early (9th day) homotypic antibody response may have been related to the persistence of an antigenic stimulus from the administration of the heterotypic TN virus 28 days before (see table 7). The feeding of SM virus to infant no. 16, in addition to producing a slight homotypic response on the 9th day and a

TABLE 3.—*Concentration of Type 1 Virus in Stools of Human Subjects Fed the SM Strain of Poliomyelitis*

Stools Collected and Pooled, Days After Virus	T.D.$_{50}$ Titer* of Fecal Material Obtained from Subject No.																			
	1		2		3		4		5		7		8		10		13		15	
	MK†	He‡	MK	He	MK	He	MK	He	MK	He	MK	He	MK	He	MK	He	MK	He	MK	He
1-4	1.5	1.7	5.5	>4.7	5.2	4.7	4.2	4.7	4.7	4.7	2.5	neg.	3.5	2.7	1.7	1.7	3.7	3.7	3.5	3.7
5-8	—	2.7	—	4.5	—	—	—	—	—	—	3.7	3.7	2.7	1.7	3.7	3.7	+	4.7	4.2	3.7
9-12	3.7	2.7	5.2	>4.7	4.5	>4.7	4.7	4.7	4.7	4.7	+	4.7	+		4.5	4.5	tox.		2.7	2.7
13-16	5.2	3.7	3.7	3.7	4.7	>4.7	5.2	3.7	4.7	>4.7	4.5	3.7	3.5	3.7	2.7	1.7	5.5	>4.7	4.2	2.7
17-20	4.5	>3.7	3.5	3.7	4.2	3.7	4.7	2.7	4.5	2.7	+	+	+		2.2	1.7	4.5	3.7	—	2.7
21-24	4.7	2.7	4.2	2.7	1.7	2.7	3.2	2.7	3.2	3.7	4.2	3.7	3.7	2.7	3.7	2.7	4.5	3.7	3.7	
25-28	4.2	2.7	2.7	2.7	1.7	3.7	2.5	1.7	2.5	2.7	+	3.7	3.7	3.7	1.2		4.5	3.7	1.7	
29-32	3.5	2.7	2.5	1.7	—	—	—		—		3.7	3.7	1.2	1.7	1.5		+	3.7	2.5	
33-36	4.0		3.7	1.7	2.2	3.7	<1.0	<3.7	2.5	1.7	2.7	2.7	neg.	1.7	3.2		2.5	1.7	1.7	
37-40	—	2.7	—	1.7	tox.	3.7	tox.	3.7	3.5	1.7	+	1.7	<1.0	1.7	2.7		+		1.7	
41-45	4.2	3.7	3.5	1.7	3.7	2.7	2.5	tox.	<1.0	3.7	1.5	1.7	<1.0	1.7	2.5		1.2		1.5	
45-48	4.5	>4.7	2.2	tox.	1.5	3.7	2.5	tox.	1.0	3.7	+	1.7	neg.	1.7	1.2		tox.		2.2	
49-52	—	4.7	tox.	1.7	<1.0	3.7	2.2	tox.	1.7	tox.	1.7	1.7	1.2	1.7	1.5		2.5	1.7	1.7	
53-56	4.2	4.7	tox.	1.7	1.0	tox.	1.5	tox.	tox.	tox.	1.2	1.7	neg.	neg.	2.7		1.5	1.7	2.5	
57-60	—		neg.	tox.	neg.	neg.	+		neg.	3.7	neg.		—	neg.	3.5		—		2.2	
61-64	2.7	>4.7	neg.	tox.	neg.	neg.	<1.0	neg.	tox.	tox.	neg.		3.0	2.7	3.5		2.7	3.7	1.7	
65-68	—	3.7	neg.	tox.	neg.	neg.	neg.	neg.	tox.	tox.	1.5		—		2.5		3.7	2.7	2.7	
69-72	3.5	3.7	neg.	neg.		neg.	neg.	tox.		neg.			neg.		2.5		—		1.7	
73-76		2.7		neg.						3.7	2.2		<1.0		neg.		1.5		neg.	
77-80	2.5	2.7								1.7	neg.		neg.		neg.		neg.		neg.	
81-84	2.7	2.7									neg.		neg.				1.5			
85-88	3.5	3.7									neg.		neg.				2.5			
89-92	neg.	1.7															+			
93-96	neg.	3.7															1.0			
97-100	<1.0	3.7															<1.0			
101-104	3.0	1.7															neg.			
105-108	neg.	1.7															neg.			
109-112	neg.	neg.															neg.			
113-116	—	neg.																		
117-120	neg.																			

* + = non-titrated virus; — = no sample; tox. = toxic; neg. = negative.
† MK = monkey kidney.
‡ He = HeLa.

gested varied from $10^{2.2}$ to $10^{5.1}$ T. C. $D._{50}$. Alimentary infection followed each feeding, and the virus was excreted for periods ranging from 55 days (infant no. 3) to 108 days (infant no. 1). A significant rise in homotypic antibody levels was observed in all cases, early in certain infants (as in no. 5) and later in others (as in no. 8).

A comparison of the figures in the last two columns with those in the sixth and seventh in table 1 indicates that there was a decrease in type 2 (except for infant no. 8) and in type 3 antibody titers during the 44 to 87 days after the feeding with the heterotypic SM virus. The difference in the case of type 3 antibody titers was greater and the decline more pronounced.

Table 2 summarizes results obtained with infants who were 175, 117, and 86 days old when given $10^{4.0}$, $10^{4.6}$, and $10^{5.5}$ T. C. $D._{50}$, respectively, of SM virus.

pronounced response on the 31st day, also seemed to stimulate a heterotypic antibody response to type 2, as evidenced by the increase in titer from <1:2 before the administration of virus to 1:16 on the 31st day after virus was ingested. The same phenomenon was not observed with respect to antibodies against type 3 virus, which decreased, in the course of 31 days, in a pattern similar to that shown in table 1. During the 37 days after the administration of type 1 virus to infant no. 18, the homotypic antibody titer rose and the type 2 antibody level remained unchanged (1:256), while antibodies against type 3 virus declined from 1:64 to 1:4.

The duration of fecal virus excretion did not seem to be influenced by the actual level of homotypic antibodies at the time the virus was administered, which ranged from <1:2 (infants 14 and 15, tables

TABLE 4.—*Administration of Type 1 (SM) Virus to Infants Less than One Month Old*

Infant No.	Antibodies Before Virus Administration: Mother Type 1	Mother Type 2	Infant (At Birth) Type 1	Infant (At Birth) Type 2	Infant (At Birth) Type 3	Virus Administration: Infants' Age, Days	Amount T.C.D.$_{50}$*	Alimentary Infection, Days	Antibodies After Virus Administration: Days After Virus	Type 1	Type 2	Type 3
22	1:712	1: 362	1:1,024	1:1,024	1:64	27	3.8	5-12	27	1:256	1:712	1:16
									52	1:178	1:256	1: 4
									65	1:256	1: 91	
17	1: 64	1:1,024	1: 64	1:1,024	1:16	22	3.5	2-34	37	1: 91	1:256	1: 4
								41-48	67	1:362	1:178	1: 4
21	1:256	1: 362	1: 712	1:1,024	1:64	20	3.8	2-29	37	1:178	1:256	1:16
									52	1:362	1:256	1:22
23	1: 64	1: 64	1: 22	1: 256	1:64	15	4.8	2-22	31	1:256	1: 22	1:11
									52	1:712	1: 16	1:11
24	1:256	1: 362	1: 256	1: 256	1:64	11	4.8	2-23	31	1:178	1: 64	1: 4
									52	1:256	1: 16	
25	1: 91	<1: 8	1: 64	<1: 2	1: 4	10	4.8	2-88	31	1: 64	1: 4	<1: 2
									52	1:256	1: 4	

* T.C.D.$_{50}$ = tissue culture doses$_{50}$, expressed as logs to the base of 10.

1 and 2) to as high as 1:362 (infant 8, table 1). The concentration of type 1 virus in fecal material was determined by the titration of stool specimens in tissue culture. The results are given in table 3 for the infants reported in table 1. In order to evaluate results properly, determinations of virus content were carried out independently in two laboratories in different cities. Tissue cultures of monkey renal epithelium were used in one, and HeLa cells in the other. Comparison of values yielded by the two methods of virus titration indicated close agreement. The highest concentration of virus in stools was found within the first 16 days after feeding, confirming observations made previously with older children.[3] After the initial 16 days, the concentrations of fecal virus seemed to decrease; however, the duration and intensity of alimentary infection varied from subject to subject, with the duration ranging from 55 days (infant no. 3) to 108 days (infant no. 1).

Administration of Type 1 Virus to Infants Less than One Month Old.—Because the results obtained in the trials described above were encouraging, the "age limit" of candidates for virus ingestion was lowered to less than one month. Six infants 10 to 27 days old were given the SM strain in oral doses ranging from $10^{5.6}$ to $10^{6.3}$ T. C. D.$_{50}$ (table 4). The levels of homotypic and heterotypic antibodies before virus administration were somewhat higher than those in older infants (tables 1 and 2). Also, curiously enough, the titers of antibodies against types 1 and 2 in the cord blood of infants no. 22 and 21 were slightly higher than in the blood of their respective mothers. However, these differences may again reflect experimental errors in the neutralization tests.

With the exception of infant no. 25, the duration of alimentary infection with SM virus in this group was shorter than in the older group (tables 1 and 2). Whether this observation may be related to the high level of maternal antibodies in infants no. 21, 22, and 24 is difficult to state. It should be noted that infant no. 8 (table 1) excreted SM virus for 74 days, although the homotypic antibody titer before feeding was 1:362, i. e., slightly higher than that of infant no. 24.

There also seemed to be some relationship between the immunologic activation of the antibody system by the ingested virus and the level of antibodies acquired from the mother. An unequivocal rise in type 1 antibody titers was noted after virus feeding in the blood samples of infants no. 17, 23, and 25, whose initial antibody levels were not very high. In the remaining three infants of this group, who had high titers of type 1 antibodies at birth, response was delayed in comparison with other infants. For instance, the titer of type 1 antibody of infant no. 22 fell from 1:1,024 at birth to 1:256 37 days after virus ingestion. On the 52nd and 65th days after feeding, almost the same levels of antibody persisted. At the same time, the heterotypic antibody titers against types 2 and 3 declined. The fall of type 1 antibodies observed in blood drawn from infant no. 21 on the 37th day after virus administration was offset by a rise on the 52nd day. Finally, there was no difference in type 1 antibody titers between specimens obtained before and after the administration of virus to infant no. 24, while heterotypic antibody titers against types 2 and 3 fell.

Since, in the past, an adequate immunologic response has always followed the establishment of alimentary infection with SM virus, there is no indication

TABLE 5.—*Repeated Administration of Type 1 (SM) Virus to Three Infants Who Failed to Develop Antibodies After First Administration of Virus*

Infant No.	Antibodies Before Virus Administration: Mother Type 1	Mother Type 2	Infant Age, Days	Infant Type 1	Infant Type 2	Infant Type 3	Virus Administration: Feeding No.	Age, Days	Days After 1st Administration	Amt. T.C.D.$_{50}$*	Excretion Days	Antibodies After Virus Administration: Days After Virus	Type 1	Type 2	Type 3
9	1:178	1: 712	At birth	1:256	1:1,024	1:64	1	24	...	2.8	None	44	1: 16	1:256	1:4
							2	70	46	2.9	None	42	1: 16	1: 91	...
							3	112	88	4.3	1-32	57	1:256	1: 64	1:4
11	1:256	1: 64	At birth	1:712	1: 16	1:16	1	26	...	3.8	None	44	1: 64		1:4
							2	68	42	4.1	3-24	42	1:256	1: 4	1:4
12	1: 64	1:4,096	26	<1: 8	1: 64	<1: 8	1	108	...	<1.3	None	44	<1: 2		
							2	152	46	4.1	3-35	42	1:362	1: 16	<1:2

* T.C.D.$_{50}$ = tissue culture doses$_{50}$, expressed as logs to the base of 10.

at present that infants less than one month old form an exception. The evidence of response may be slightly delayed in the youngest age group, particularly in cases where the level of congenitally acquired antibodies is very high.

Repeated Administration of Type 1 Virus.—Administration of $10^{2.8}$ T. C. D.$_{50}$ of SM virus to two infants who were 24 and 26 days old was not followed either by evidence of alimentary infection or by a rise in homotypic antibodies (no. 9 and 11, table 5). In addition, another infant 108 days old (no. 12) failed to become a carrier, and there was no rise in the level of type 1 antibodies after the administration of one drop of SM virus in 4 ml. of formula. The concentration of virus in the mixture was lower than the equivalent of $10^{2.9}$ T. C. D.$_{50}$.

To determine whether immunization failure was directly related to the small amount of virus in the ingesta, these three infants were given another virus feeding (table 5). This time no. 11 and 12 received $10^{4.1}$ T. C. D.$_{50}$ of virus, whereas the dose for no. 9 was kept low ($10^{2.8}$ T. C. D.$_{50}$). Subjects no. 11 and 12 promptly became intestinal carriers, and a marked rise in circulating type 1 antibodies followed. Infant no. 9 again failed to become an alimentary carrier, and his level of type 1 antibodies remained unchanged for 42 days. Finally, after a third feeding consisting

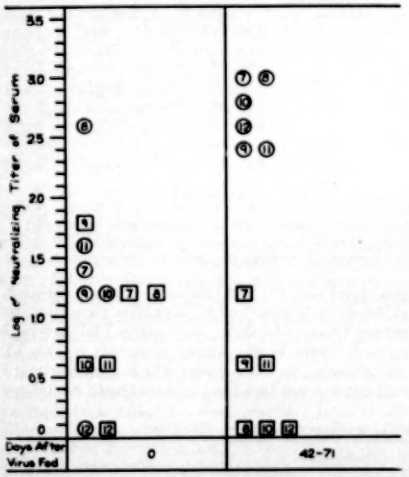

Fig. 1.—Increase of homologous antibodies after feeding type 1 with no simultaneous increase of type 3 antibodies. Numbers in circles, number of subject with antibodies against type 1; numbers in squares, number of subject with antibodies against type 3. Ages in months of infants at date of feeding were 1 (no. 8), 2 (no. 10 and 11), 2½ (no. 7), 3½ (no. 9), and 5 (no. 12).

of $10^{4.9}$ T. C. D.$_{50}$ of virus, both alimentary infection and a rise in homotypic antibodies were achieved.

Although these data are of meager statistical value, neither the age of the infants nor antibody status at the time of virus administration appeared to be responsible for the three "immunization failures." The roles of the relatively small amount of virus ingested and of some other possibly preexisting factor that may have prevented the virus from reaching a multiplication site in the intestinal tract may have to be considered (see Comment, below).

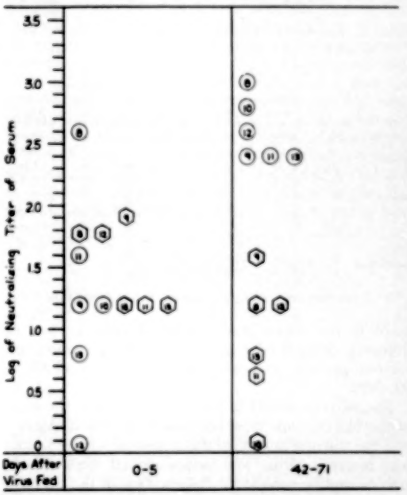

Fig. 2.—Increase of homologous antibodies after feeding type 1 with simultaneous decrease of type 2 antibodies. Numbers in circles, number of subject with antibodies to type 1; numbers in hexagons, number of subject with antibodies to type 2. Ages in months of infants at date of feeding were 1 (no. 8), 2 (no. 10, 11, and 13), 3½ (no. 9), and 5 (no. 12).

Fate of Homotypic and Heterotypic Antibodies.—The antibody titers in the serums of seven infants who received the type 1 virus are presented diagrammatically in figure 1 (infants no. 7-12) and figure 2 (infants no. 8-13). The clinical histories of these infants have been summarized in the preceding section of this report.

Figure 1 shows that after the administration of SM virus there was a marked rise in homotypic antibody titers. The rise was least significant in infant no. 8, whose serum showed a high level of congenital antibodies before the administration of virus. Within the observation period (42-71 days) antibodies against type 3 virus declined or remained the same.

Data on type 2 antibodies are presented in figure 2. In this case, the rise in homotypic antibody level was not accompanied by as marked a drop in type 2 as in type 3 antibody titers (see fig. 1). The serum antibody titer of infant no. 10 against type 2 virus fell to zero, while the decreases in the remaining serums were not of the same magnitude.

Lack of Contagiousness of SM Virus.—In clinical trials described elsewhere,[3] transmission of fecal SM virus occurred in very few cases and only after a rather intimate contact between "donors" and "recipients." The same question was investigated on a smaller scale under the conditions of the present study.

Seven of the infants whose clinical histories appear in either table 1 or 5 were placed in the same nursery with babies no. 10 and 14, who were 22 and 26 days old respectively. Both type 1 and type 2 antibodies were present in the blood of no. 10, but no. 14 had antibodies to type 2 and none to type 1. As seen in table 6, the donor group received type 1 virus in different dosages. All became intestinal carriers for various periods, in some cases for as long as 70 to 99 days.

TABLE 6.—*Absence of Transmission of Infection to Infants Kept in Same Room with Those Fed Type 1 (SM) Virus*

Group	Infant No.	Type 1 Antibodies Before Virus	Date Placed in Nursery, 1956	Amount of Virus Fed T.C.D.$_{50}$*	Alimentary Infection, Days	Date Released from Observation, 1956	Type 1 Antibodies at Release
Donors	7	1: 6	1/16	5.1	1-74	4/23	1:1,024
	13	1: 16	1/16	5.1	1-90	5/31	1:1,024
	8	1:362	1/16	2.8	1-74	4/23	1:1,024
	11	1: 44	3/ 2	4.1	3-24	4/23	1: 256
	12	<1: 2	3/ 2	4.1	3-35	4/23	1: 362
	15	<1: 8	3/ 2	4.1	3-70	5/29	1:1,449
	9	1: 16	4/ 9	4.3	1-32	6/ 4	1: 256
	10	1: 91	1/16	None	None	3/ 2	1: 16
Contacts	14	<1: 2	1/16	None	None	5/16	<1: 2

* T.C.D.$_{50}$=tissue culture doses$_{50}$, expressed as logs to the base of 10.

The nursery was 24 ft. long by 14 ft. wide. The cribs of the two contacts were kept between cribs of donors, and the nursing personnel did not know which infants had received virus. The nurses moved from crib to crib in routine care of the babies. One of the contacts (no. 10) was kept in the nursery for one and one-half months (table 6), during which time donor infants no. 7, 13, and 8 were excreting type 1 virus frequently and in quite high concentration (see table 3). The other infant, no. 14, was kept in contact for four months. Although stools were tested daily for the presence of fecal virus, none was isolated from the feces of either no. 10 or no. 14 during the time they were exposed to the virus excreted by the seven donors. The absence of alimentary infection with type 1 virus was further confirmed by a decrease of homotypic antibody in the blood of no. 10 and by the fact that no type 1 antibody developed in no. 14. Later, administration of SM virus to both of these infants was followed by alimentary infection and homotypic antibody rise (tables 1 and 2).

Administration of Type 2 Virus.—Infants who were born of mothers immune to type 2 and who possessed type 2 antibodies themselves, as shown in table 7, received the type 2 TN strain. One of the infants, no. 15, was given 30 drops of glycerinated suspension of mouse cord and brain representing $10^{8.9}$ P. D.$_{50}$ of virus; and the other three, no. 14, 19, and 20, received 30 drops of a more diluted preparation representing only $10^{7.9}$ P. D.$_{50}$ of virus. Two of the four infants excreted type 2 virus, which was isolated in monkey kidney tissue culture. Since the TN strain previously had been found to be noncytopathogenic for monkey kidney tissue culture,[5] this finding was rather unusual and possibly may be related to the multiplication of the virus in a very young organism.

A specific rise in type 2 antibodies was observed in the blood of infant no. 15. The same antibody level was maintained in the blood of infant no. 20 for 67 days after virus administration. Type 2 antibody titers in the blood of infants no. 14 and 19 on the 37th day after virus feeding were either lower than those observed prior to virus ingestion (no. 19) or at the same level (no. 14) and remained relatively constant, as shown by tests 59 and 67 days after virus administration. Conversely, there was a marked fall in type 3 antibody titers in the serums of infants no. 14, 15, and 20 during the same period. The heterotypic type 1 antibody was not found in blood obtained from infants

TABLE 8.—*Persistence of Homotypic Antibodies After Oral Administration of Attenuated Poliomyelitis Viruses to Infants*

Infant No.	Antibodies Before Virus Administration: Type 1	Type 2	Type 3	Virus Administration: Type	Age in Days	Antibodies After Virus Administration: After Virus Days	Mo.	Type 1	Type 2	Type 3
1	1:64	1: 91	<1: 8	1	84	66	7	1: 712	1: 23	<1:8
							7	1: 256		
2		1: 23		2	153	18			1:1,024	
							5		<1: 128*	
	1:44	1:178	<1: 2	1	83	59		1: 362	1: 64	
4							7	1: 256		<1:2
		1: 64		2	145	18			1: 64	
							5		1: 91	
	1:64	1: 64	1:64	1	67	59		1: 712	1: 16	1:8
3							7	1:1,024		<1:2
		1: 16		2	125	18			1: 362	
							5		1:1,024	
	1:23	1:256	1:16	1	49	77		1:1,024	1: 64	1:4
5							7	1:1,024		<1:2
		1: 44		2	111	18			1: 64	
							5		1: 3	
1	1: 4	1: 16	1:16	1	35	66		1: 256	<1: 8	<1:8
							7	1: 256	1: 16	1:4
13	1:16	1: 16	<1: 2	1	51	44		1: 256	1: 6	
							4	1:1,024	1: 16	<1:2

* Serum sample insufficient for repetition of the test.

TABLE 7.—*Administration of Type 2 (TN) Virus to Infants at Age of Two to Five Months*

Infant No.	Antibodies Before Virus Administration: Mother Type 1	Mother Type 2	Infant Age, Days	Infant Type 1	Infant Type 2	Infant Type 3	Virus Administration: Age of Infant, Days	Amount P.D.$_{50}$*	Antibodies After Virus Administration: Days After Virus	Type 1	Type 2	Type 3
14	1:8	1:256	17	<1:8	1:256	1:256	147	2.8	37	1:256†	1: 16	1:16
			143	<1:2	1: 16				59	1:362‡	1: 11	>1: 44
15	1:4	1: 78	At birth	<1:2	1: 94		73	5.3	44	<1: 2	1:1,024	1: 4
			73	NT	1: 16	1: 11						
19	<1:2	1:712	At birth	<1:2	1:712		94	2.8	37	<1: 2	1: 64	<1: 2
			94	NT§	1:256	<1: 2			67	<1: 2	1: 64	
20	NT	NT	At birth	<1:2	1:362	1: 64	89	2.8	37	<1: 2	1: 256	1: 6
			89	NT	1: 64				67	<1: 2	1: 256	1: 4

* P.D.$_{50}$=mouse paralytic dose$_{50}$, expressed as logs to the base of 10.
† 9 days after administration of type 1 (SM) virus (see table 2).
‡ 31 days after administration of type 1 (SM) virus (see table 2).
§ Serum used up.
‖ NT=not tested.

no. 15, 19, and 20. Thus, one may assume that an immunologic response to TN virus occurred in infants no. 15 and 20 and probably in the other two infants. Determination of antibodies after a longer interval may dispel any doubts on this point.

Persistence of Immunity.—Serum samples were secured from five infants seven months and from one four months after the administration of type 1 virus (table 8). With two exceptions, no. 1 and 13, the same subjects also received TN (type 2) virus at the ages shown in table 8.

Data in the last three columns of table 8 indicate that feeding of type 1 virus was obviously responsible for the persistence of a high level of homotypic antibodies throughout the four-to-seven-month observation period. This is fully substantiated by the fact that during the same interval the type 3 antibody titers (last column, table 8) in every case except one dropped to <1:2. The point is even more clearly illustrated in figure 3, in which the rise in type 1 antibodies of five infants is contrasted with the simultaneous decrease or lack of increase in heterotypic type 3 antibodies.

After the administration of TN virus, there was a slight rise of type 2 antibody titer in infant no. 4 and a considerable rise in infant no. 3, whereas, during the five-month observation period, type 2 antibodies declined in the blood of infants no. 5. After an initial drop, there was a slight increase in the levels of type 2 antibodies in infants no. 1 and 13, who had received type 1 virus alone seven and four months previously. This may represent a remnant of heterotypic response to the type 1 feeding (see table 1), or it may indicate possible exposure to type 2 virus. However, no attempt was made to isolate fecal virus after the excretion of type 1 virus ceased, and no definite statement can be made. Clinical follow-up of these infants revealed normal development.

Comment

The results obtained in this study have shown that a single administration by the oral route of attenuated poliomyelitis virus to infants less than 6 months old will elicit alimentary infection and will activate an immunologic response, irrespective of the presence of passively transferred serum antibodies to the virus fed. Virus was fed to 24 infants; 16 received the SM (type 1) virus alone, 2 received the TN (type 2) virus, and 6 received both viruses administered weeks or months apart. Careful pediatric and nursing care of the infants failed to reveal objective signs of any ill-effects attributable to the ingestion of poliomyelitis virus. All of the infants who received the viruses at different ages showed gain in weight comparable to infants who were not fed virus.

Ingestion of type 1 virus was followed by prompt establishment of alimentary infection. That tissues of an infant 10 days old are able to support growth of poliomyelitis virus is not surprising per se, since cases of poliomyelitis infection with virulent virus have been described in infants shortly after birth after possible intrauterine infection.[6] A number of cases of poliomyelitis in infants less than a year old have also been reported in medical literature.[7]

Intestinal mucosa of children 6 to 15 years old previously has been found to be susceptible to direct infection with two plaque-forming particles of SM virus administered in a capsule.[2] This method of virus administration could not be applied in the present study, and virus feeding in liquid form was substituted. The results, though few in number, suggest that the inoculum had to exceed considerably two plaque-forming particles of virus in order to induce uniform alimentary infection in infants less than one month old. Although the number of infants fed virus at that age was too small to permit definite conclusions, SM virus in concentrations in excess of $10^{-5.0}$ T. C. $D._{50}$ seemed to prove uniformly infectious and immunogenic.

The seemingly higher resistance of younger infants may depend upon two factors. One could be related to a specific difference in cell physiology during the first month of life. Thus, in a baby 30 days old or less,

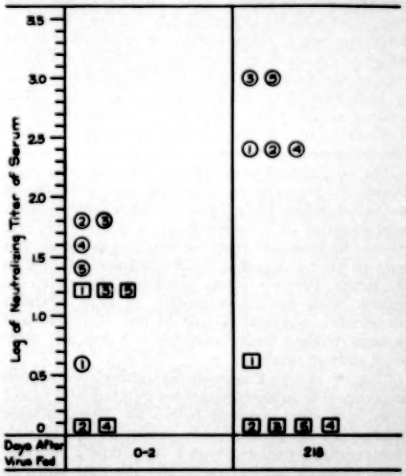

Fig. 3.—Increase of homologous antibodies after feeding type 1 with no simultaneous increase of type 3 antibodies. Numbers in circles, number of subject with antibodies to type 1; numbers in squares, number of subject with antibodies to type 3. Ages in months of infants at date of feeding were 1 (no. 1), 2 (no. 3 and 5), and 3 (no. 2 and 4).

the virus-cell relationship may not be the same as that in older infants and children and may adversely affect the rate of multiplication of the virus, viz., infant no. 22 (table 4), who excreted the virus only between the 5th and 12th days after feeding. A direct relationship between age and susceptibility to poliomyelitis infection has been observed in laboratory animals,[8] and the relative infrequency of poliomyelitis infections among young infants has been noted.[7]

The second factor to be considered is the amount of congenitally acquired homotypic antibodies. The concentration of these was higher in infants at the age of 30 days than in older infants and children or after administration of immune serum globulin.[9] However, in studies on passive-active immunization of primates, Bodian[9] observed that the presence of

passive antibodies, even at high levels, did not interfere with the establishment and course of alimentary infection with poliomyelitis virus but did prevent viremia and invasion of the central nervous system. In the present study, no. 22 was the only infant who had a titer of passive antibodies to type 1 as high as 1:1,000, which may be related to the short duration of SM virus excretion in his case.

Serum antibody titers of the two infants (no. 9 and 11, table 5) who failed to develop alimentary infections after the first administration of a small amount of virus or of those who showed a slightly delayed rise in antibodies after virus administration were also high in comparison with those of the remaining subjects (table 1) of the same series. From present data, it appears doubtful that in infants less than one month old a high titer of passive antibodies will consistently prevent alimentary infection with a small amount of type 1 virus. Because of the small number of subjects in this trial, it was not possible to determine what concentration of antibodies might influence the duration of alimentary infection. Whichever of the factors—relative lack of susceptible cells or high titer of serum antibodies—was in operation, feeding of adequate amounts (in excess of $10^{-3.0}$ T. C. D.$_{50}$) of SM virus resulted in inapparent infection and immune responses.

The administration of type 2 (TN) virus to eight infants led to a rise in homotypic antibody titers in the blood of five. The response of the remaining three, who received $10^{2.8}$ mouse P. D.$_{50}$ of the virus, will have to be evaluated from the results of neutralization tests to be performed on blood samples collected in the future. The two factors mentioned above (in connection with the administration of type 1 virus) conceivably may play a role in this case also, and perhaps feeding larger amounts of virus will yield more uniform results.

Changes in type 2 neutralizing antibody levels such as occurred in subjects who were infected with type 1 virus have been reported before by several investigators.[10] In the present study, among 16 infants who received the attenuated type 1 virus, type 2 antibody titers increased in five cases and the titer failed to decline in two additional cases. The heterotypic rise was maintained in the blood of two infants four and seven months after administration of type 1 virus (table 8). Similar changes did not occur in type 3 neutralizing antibodies, which were found to decline gradually and which reached levels below detection in the blood of infants at the age of 7 to 10 months. There was also no effect on the development of type 1 antibodies after administration of type 2 virus to three infants who had no preexisting type 1 antibodies. Thus, it may be concluded within the limits of these data that a response to SM virus feeding may be broader than a response solely to the type causing alimentary infection.

With the current trial included, attenuated strains of poliomyelitis virus have been given to infants, children, adolescents [11] and to adults (Sabin [12]). As far as can be judged, none of the subjects belonging to these different age groups showed any ill-effects that could be attributed to the ingestion of live virus.

For a more extensive clinical trial, the youngest age group is the most desirable, since it represents a relatively immobile population in which the possibility of transmission of the virus from one subject to another is more remote (see table 6). The presence of passive immunity will not prevent an active response if an adequate amount of virus is administered, and "blending" of the two types of immunity may circumvent the danger of exposure to virulent virus at an age when congenitally acquired antibodies tend to diminish or disappear. Follow-up studies over a much longer period of time may indicate or give substance to the hope that the level of homotypic antibodies induced by the ingestion of virus in the first year of life may confer permanent protection.

Summary

Living attenuated poliomyelitis virus was administered by the oral route to 24 infants. Sixteen received SM (type 1) virus alone, two the TN (type 2), and six both viruses at different times. All the infants were under 6 months old; the ages of six were between 10 and 27 days. Most of them had antibodies acquired from their mothers to the virus fed. All infants developed active immunity after inapparent alimentary infection. High levels of homotypic antibodies caused by the feeding of virus were maintained during an observation period of seven months.

Box 149, N. Middletown Rd. (Dr. Koprowski).

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FETAL MORTALITY IN CESAREAN SECTION

Moses Grossman, M.D.
and
Ralph C. Benson, M.D., San Francisco

• *The gross fetal mortality associated with cesarean sections ranged from 4.5 to 15.6% in 13 institutions. The causes of death and indications for sections have been reviewed in detail for the last 16 years, covering 569 sections, at University of California Medical Center. The maternal mortality has been reduced by such factors as briefer trials of labor, blood transfusion, and new surgical techniques, but the fetal mortality has not shown corresponding improvement. Erythroblastosis, congenital anomalies, and atelectasis with its complications accounted for many deaths occurring within an hour after birth. Prematurity, however, is the largest single contributing factor to the high mortality rate. An accurate appraisal of arrival at term is important in order that a premature infant will not be delivered by ineptly timed and purely elective section.*

A striking and continued reduction has occurred in maternal morbidity and mortality after cesarean section, as a result of medical advances in the past two decades; however, fetal salvage has not improved encouragingly. With increasing safety for the mother, popularization of cesarean section logically followed. Nevertheless, when it became apparent that operative delivery from above did not necessarily insure the survival of a healthy infant, a more conservative attitude developed with regard to indications for and timing of cesarean section.

The obstetrician need not be reminded of his obligation to both mother and infant for safe delivery. The obvious risks of prematurity must be accepted, however, when an urgent maternal indication for cesarean section is present. Yet, in cases where hasty elective surgery is performed for borderline disproportion or when repeat section is done too early, the supposed term child is occasionally immature and frequently dies. As a consequence, the fate of the infant after cesarean section is of timely and vital importance. We have, therefore, reviewed the experience with cesarean section at the University of California Medical Center, San Francisco, for the past 48 years, with special consideration of the period 1940-1955, inclusive, in an attempt to answer the question, "Does cesarean section insure the delivery of a normal, living child who will survive?"

For purposes of review and comparison, the uncorrected fetal mortality in a number of large published series is summarized in table 1. The high figures are quite startling. The notable factors in this series are the high incidence of premature infants and the mortality associated with the obstetric pathology that necessitated the section, as opposed to the increased hazard of abdominal delivery. Correction for these two elements would make a comparison of fetal mortality after vaginal delivery more meaningful, but we must look to the statistics in elective sections to supply these answers. Wolff and Roter,[1] reporting on 162 elective sections where a previous cesarean was the indication, indicated a mortality of 3 (1.85%) and morbidity of 17 (10.4%).

Cesarean sections performed on clinic and private patients at the University of California Medical Center in San Francisco for the past 48 years have been reviewed (fig. 1). Our experience with respect to maternal morbidity and mortality essentially parallels that of other centers. This was reported in part previously by Arnot[2] and King.[3] The introduction of antibiotics, improved methods of anesthesia, and obstetric advances have almost eliminated maternal mortality (one maternal death since 1938—a pregnancy complicated by disseminated lupus erythematosus) and have materially reduced maternal morbidity. A striking contrast between maternal and fetal mortality, however, is shown in figure 2. As the number of deliveries and cesarean sections has increased, the absolute number of deaths in infants has steadily climbed. These data are expressed in terms of percentage of infant mortality, and figure 3 clearly indicates that (1) infant mortality in cesarean section has shown little improvement over the years and (2) the mortality is still an appreciable and serious one. It would appear, therefore, that the risk of cesarean section is still considerable if the welfare of the mother and the infant are regarded critically. A comparison of fetal loss in deliveries by cesarean section with total fetal experience over a 10-year period shows that the gross perinatal mortality of babies delivered by cesarean section was 8.3% (corrected, 2.5%); the gross infant mortality was 2.5% (corrected, 1.8%); and the gross neonatal mortality was 0.8% (corrected, 0.6%). In order to shed further light on this problem of fetal mortality, our experience at the University of California Medical Center in San Francisco is reviewed in detail from 1940 to 1955 inclusive.

Obstetric Factors

As in other centers, infants have been lost here after surgical delivery who, we now believe, might have survived. An analysis of the causative factors is revealing. The method of cesarean section, as well as the type of anesthesia, plays a part in fetal mortality and morbidity. Table 2 discloses the types of operation used during the past 16 years, together with the method of anesthesia used. A graphic representation of the type of cesarean section done at this institution during the 48-year period, 1907 through 1954, is of

From the Department of Pediatrics and the Department of Obstetrics and Gynecology, University of California Medical Center. Dr. Benson is now at the University of Oregon Medical School, Portland, Ore.

interest. Figure 4 demonstrates the shift from the classic to the low cervical procedure after 1924. The Porro operation (subtotal postcesarean hysterectomy), frequently used early in this series in septic cases, was all but forgotten for a time after 1924, when briefer

TABLE 1.—*Neonatal Mortality (Uncorrected) in Cesarean Section (from the Literature)*

	Yr.	No. of Sections	Gross Fetal Mortality %
Bellevue Hospital (Stubblefield and Decker; Bull. New York Acad. Med. 29:640-654 [Oct.] 1953)	1942-1951	654	8.8
Boston Lying-in Hospital (Irving; Am. J. Obst. & Gynec. 39:680-690 [Dec.] 1945)	1934-1943	1,887	15.6
Bethel Hospital, Brooklyn (Litchfield and others; J.A.M.A. 151:783-785 [March 7] 1953)	1945-1951	909	4.5
Chicago Lying-in Hospital (Potter and Adair; Am. J. Obst. & Gynec. 45:1054-1065 [June] 1943)	1931-1941	1,402	8.7
City of New Orleans (King; Am. J. Obst. & Gynec. 40:800-809 [Nov.] 1940)	1927-1936	1,108	10.8
Johns Hopkins Hospital (Manahan; Connolly, and Eastman; Am. J. Obst. & Gynec. 44:1059-1069 [Dec.] 1942)	1896-1942	1,333	7.7
Los Angeles County Hospital (Hibbard and Kroener; West. J. Surg. 64:485-488 [Sept.] 1956)	1949-1953	1,375	8.7
Methodist Hospital, Brooklyn (Arber; Am. J. Obst. & Gynec. 53:927-935 [June] 1947)	1936-1946	768	4.9
Lying-in Hospital, New York (Landesman; Am. J. Obst. & Gynec. 61:557-564 [March] 1951)	1933-1949	1,834	7.7
Lying-in Hospital, Philadelphia (Mohler; Am. J. Obst. & Gynec. 45:466-478 [March] 1943)	1932-1937	665	10.2
Lying-in Hospital, Philadelphia (Mohler; Am. J. Obst. & Gynec. 43:466-478 [March] 1943)	1937-1942	657	9.2
Tennessee Chyllan Hospital (Riddle and others; Am J Obst. & Gynec. 63:967-977 [May] 1952)	1949-1952	703	11.5
University of California Medical Center, San Francisco	1940-1955	509	8.2

trials of labor, blood transfusion, and improved surgical techniques became the rule. Later, cesarean hysterectomy came to be used more for the elimination of a tumorous or defective uterus, or for sterilization, rather than for the control of intrapartum intrauterine

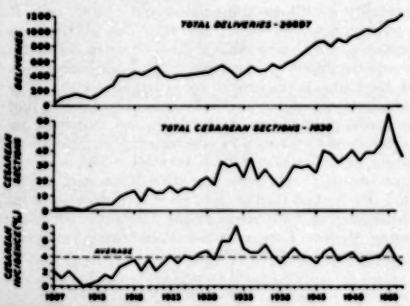

Fig. 1.—Cesarean sections performed at University of California Medical Center, 1907-1955.

infection. The extraperitoneal cesarean section has not been commonly used here, because most of the patients have been registered and followed in this clinic. Only a few gravidas are admitted each year to the obstetric service after a prolonged or neglected labor, failure of forceps delivery, or other emergency circumstances. The increased use of the classic operation after 1944 is, in part, a reflection of the increasing numbers of repeat sections done electively prior to the onset of labor, where there is a lack of development of a thinned lower uterine segment.

The changing aspects of obstetric philosophy, new concepts, modification of hospital policy and staff, as well as individual consistency of action, all play a part in the decision to effect or to avoid cesarean section. It would be impractical to speculate on each of these and other facets of the problem here. Suffice it to say,

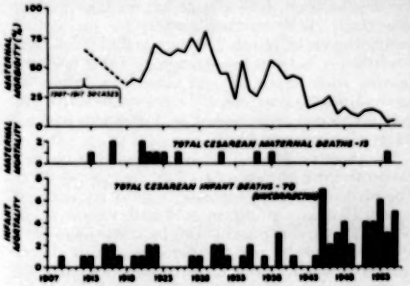

Fig. 2.—Maternal and fetal mortality of cesarean sections performed at University of California Medical Center, 1907-1955.

our cesarean section incidence of 3% (1955) indicates an over-all conservatism.

Objections are seldom voiced to the decision to do a cesarean section for severe grades of abruptio placentae or placenta previa, especially in the primigravida. However, we believe the physician can be declared hasty in terminating pregnancy near term for slight or even moderate antepartum bleeding, when bed rest, supportive therapy, and avoidance of needless intervention might permit the vaginal delivery of a larger, more mature child two to three weeks later.

TABLE 2.—*Type of Cesarean Section and Anesthesia (1940-1955, University of California Medical Center)*

Cesarean Section	No.
Classic	27
Low flap	16
Cesarean hysterectomy	2
Extraperitoneal	2
	47
Anesthesia:	
Local infiltration	23
Cyclopropane	8
Spinal	6
Thiopental (Pentothal) sodium	5
Nitrous oxide and ether	5
Caudal	0
	47

When we recall that the infant gains about 10 oz. per week during the last month of gestation, time becomes a valuable ally.

The correct estimation of "term" in pregnancy is frequently inaccurate, even with a fairly reliable menstrual history. The most experienced obstetician often miscalculates the maturity of the infant in utero. We have noted that clinicians overestimate, rather than underestimate, the weight of the unborn child. Roent-

genographic appraisal of fetal age, although fraught with variables and not always satisfactory, often can be of help in the timing of elective section.[4] For example, if proximal tibial and distal femoral epiphyses are not well visualized, further delay of surgery might be prudent, even though the dates themselves suggest a more advanced pregnancy. Cephalopelvic disproportion often indicates the need for surgical delivery. A trial of labor, however, should be required in borderline cases, especially when there are possible compensatory factors. Planned cesarean section prior to the onset of good labor at term has often been unnecessary and has resulted in the delivery of an immature infant. This applies also, we have found, to

Fig. 3.—Infant mortality in cesarean sections, 1907-1955.

repeat cesarean section. A retrospective consideration of the indications for cesarean section in the 47 fatal deliveries between 1940-1955 shows that in 44 cases section was indicated from the patient's record; in 31, the timing was seemingly correct; in 9, section might have been done earlier; and in 4, section might have been postponed as baby was not at term (previous section only index used). In all fairness to the obstetricians involved, it must be admitted that a clinical situation may appear quite different in later review, particularly when only the history is available for subsequent appraisal. Nevertheless, it is our considered opinion that, in the greater interest of the child, certain of the operations probably should have been accomplished earlier and others delayed.

TABLE 3.—*Causes of Death in Twenty-seven Babies Who Lived One Hour or More (1940-1955, U. C. Medical Center)*

Atelectasis, including hyaline membrane and aspiration:		
Cause of death		14
Contributory	3	
Hyaline membrane	9	
Aspiration, massive	1	
Erythroblastosis		
Cause of death		5
Contributory	1	
Serious congenital anomalies		5
Diaphragmatic hernia	2	
Hydrocephalus	1	
Imperforate anus	1	
Anomalies of respiratory tree	1	
Nonviable (less than 800 gm.)		2
Intracranial hemorrhage		1

Fetal Factors

Over the last 16 years (1940-1955), 569 cesarean sections were performed with a total of 47 fetal deaths—a gross perinatal mortality of 8.2%. With correction for congenital anomalies incompatible with life, nonviable babies (less than 800 gm. [1.75 lb.]), erythroblastotic infants, and babies who died in utero before or during the operation, there were 15 deaths in 537 cases, or a corrected mortality of 2.9%. Of the 569 sections performed, 20 infants were either born dead or had never established respiration. Twenty-seven lived an hour or more, 16 were premature (weight under 2,500 gm. [5.5 lb.]), and 11 were full term; 20 were male and 7 female. The average length of life for the 27 babies was 2.5 days, the median being 1.7 days.

Table 3 relates the cause of death in the 27 babies who established respiration and lived an hour or more. Slightly more than half of this group died of respiratory causes, with hyaline membrane disease high on the list. This might be expected from the fact that more than one-half of these babies were premature. The six cases of erythroblastosis occurred during a one and one-half year period between 1946 and 1947, when cesarean sections were done before term (34-38 weeks) in instances where severe hemolytic disease of the newborn was suspected in the baby. This was before the use of the exchange transfusion became estab-

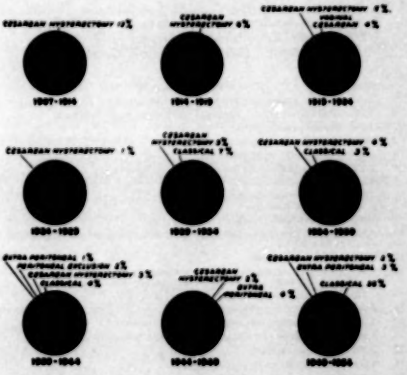

Fig. 4.—Type of cesarean section, 1907-1954.

lished. Thus, delivery by cesarean section of these babies served to superimpose prematurity onto the already existing hazard of erythroblastosis. With the use of cesarean section, our salvage of these babies was very poor and the procedure was abandoned. One of the six babies who died had hyaline membrane disease, and this, rather than erythroblastosis, was undoubtedly the cause of death. In the group of babies with congenital anomalies, it is interesting to note that both babies who died of diaphragmatic hernia were siblings, born a year apart. Of the two nonviable newborn infants, one weighed 780 gm. (1.75 lb.) and the other 450 gm. (1 lb.); the latter was, in fact, a deliberate therapeutic interruption of pregnancy. In spite of its small weight, the baby breathed and survived for 15 hours.

Table 4 lists the 20 babies who did not establish satisfactory respiration. Almost all of these were born dead. There were 10 males and 10 females in this group; 9 were premature and 11 full term.

Of the 47 cesarean sections fatal to the infants, 14 were elective. The cause of death in these babies is shown in table 5. This group of babies should be considered critically in any series, because it generally excludes the serious obstetric catastrophes. Preventable deaths are apt to be found here as they were in our own series.

We have already mentioned the erythroblastotic babies in commenting on table 3. The three newborn infants who died of atelectasis, including hyaline membrane disease, were all infants who were considered to be at term, both by date and by palpation of the fetus. Cesarean section was done electively, the only indication being a previous section. At the time of delivery, all three of these babies were found to be small; two of them died of hyaline membrane disease and one of primary atelectasis. If the operative delivery had been postponed for several weeks in these cases, the outlook for survival of the babies would have been improved considerably.

TABLE 4.—*Indications for Section in Twenty Babies Who Never Established Respiration (1940-1955 University of California Medical Center)*

Baby No.	Wt. (Gm.)	Indications for Section
1	2,840	Partial premature separation of placenta
2	2,320	Obstructed labor; myoma; child dead before section
3	1,300	Severe preeclampsia
4	5,020	Prediabetic with eclampsia
5	4,800	Prediabetic with eclampsia
6	2,250	Partial premature separation of placenta
7	2,480	Premature desultory labor
8	2,080	Erythroblastosis, preeclampsia Previous section
9	1,260	Severe preeclampsia
10	1,900	Polyhydramnios, previous caesarean section (fear of rupture of uterus)
11	2,130	Compound breech
12	490	Diabetic; intercapillary glomerulosclerosis (Kimmelstiel-Wilson disease); pregnancy interrupted; sterilization
13	700	Partial premature separation of placenta
14	3,300	Massive intraperitoneal infection
15	2,800	Partial premature separation of placenta
16	2,300	Severe preeclampsia, premature separation of placenta
17	3,600	Ruptured uterus
18	2,580	Cervical fibroid; achondroplast
19	2,300	Sibling 18; achondroplast Section done early, mother suicidal
20	3,680	Severe complete premature separation of placenta; baby dead on admission to hospital

Table 6 lists the indications for cesarean section and the perinatal mortality for each indication over the last 16-year period for all cesarean sections performed. Corrections for infant mortality have been made by excluding babies who were known to be dead before the section was completed, babies who had congenital anomalies incompatible with life, and babies who were considered nonviable (less than 800 gm. [1¾ lb.]). The most common indication, by far, in this group was a previous section, and the mortality here was not a great deal higher than in the over-all obstretic experience for a comparable period.

The group with cephalopelvic disproportion was considerably smaller in our series than in most published studies from eastern teaching hospitals. This is hard to explain, although certain related factors might be a lower incidence of rickets in San Francisco and basic population differences.

As in other reported series, the group with the highest mortality was that in which premature separation of the normally implanted placenta necessitated an emergency cesarean section. The gross mortality figure of 62.5% for this group is more representative of what takes place than the corrected figure of 12.5%. The correction represents the eight babies who died

TABLE 5.—*Causes of Death of Fourteen Infants Delivered by Elective Cesarean Section (1940-1955, University of California Medical Center)*

Erythroblastosis fetalis	5
Atelectasis, including hyaline membrane (these infants weighed 1,980, 2,300, and 2,800 gm.)	3
Polyhydramnios	1
Monstrosity	1
Nonviable fetus (450 gm.: late therapeutic abortion)	1
Diaphragmatic hernia	1
Baby dead in utero, previous cesarean section	2

of the separation before they could be delivered, the cause of death being the separation itself. In our experience, it would be more fair to state that, where serious separation of the placenta had occurred, the mortality was approximately 60%. Another group with high fetal loss was that in which cesarean section was performed because of toxemia and hypertensive disorders, but, in these cases, the maternal indication for delivery was most pressing.

Comment

Examination of infant perinatal and neonatal mortality rates in the United States over the past 50 years discloses the fact that today most infants are lost in the first three days of life. Bundesen [8] has stated that in the United States more infants now die in the first three days of life than during the remaining 362 days of the first year. He quotes the special committee on infant mortality of the Medical Society of the County of New York as stating that "The persistently high

TABLE 6.—*Cesarean Section Indication and Total Infant Deaths (1940-1955, University of California Medical Center)*

Indication	Total No.	Gross Deaths	Gross Rate, %	Corrected Deaths	Corrected Rate, %
Previous cesarean section	302	11	3.6	5	1.6
Contracted pelvis and/or disproportion	68	5	7.3	1	1.4
Placenta previa	34	3	8.8	2	5.9
Previous critical pelvic surgery	33	0	0	0	0
Toxemia and hypertensive disorders	29	10	34.4	4	13.8
Elderly primigravida	25	0	0	0	0
Prolonged and/or desultory labor	20	0	0	0	0
Premature placental separation	16	10	62.5	2	12.5
Breech presentation	5	1	20.0	0	0
Diabetes mellitus	6	1	16.6	0	0
Rh sensitization	4	3	75.0	0	0
Postmaturity	4	0	0	0	0
Other	45	3	6.6	1	2.2

perinatal mortality rates stand foremost among the urgent problems on the agenda of Public Health workers." We would add to this: "and of obstetricians and pediatricians."

In examining the causes for the high perinatal mortality and, specifically, the reasons for no decline in recent years, one must focus attention particularly on the special groups of babies who contribute to this loss. Foremost among these are the premature infants,

but another important group is that which has been examined in the preceding tables, i.e., the babies born by cesarean section. Their gross perinatal mortality of 8.2% is more than three times that of the gross infant mortality of all groups. The two outstanding causes for this high mortality are (1) prematurity and (2) depression of the fetal respiratory center brought on by hypoxia or toxic states of the mother.

Prematurity is frequently unavoidable. The situation is often one of obstetric catastrophe, such as abruptio placentae with supervening massive hemorrhage, which necessitates immediate delivery—preferably by section. Thus, the baby arrives quite prematurely, sometimes before it is viable, or at the state of maturity where the chances for survival today are not much more than 50%. However, among this group of "unavoidable prematures," one must recognize a smaller category but, nevertheless, one about which something can be done—namely, those who, through an error in dates and misjudgment of fetal weight and maturity, are delivered prematurely by elective section (three in our series). The loss of these babies, in a situation where prematurity plays an important role in their death, is truly an avoidable tragedy. One of the sad obstetric realities is that we are, as yet, ignorant about the causes of the onset of labor. It is difficult, moreover, to know when a woman has arrived at term. We believe it is better to allow the woman to go into labor, in most instances, and to perform the operation as soon as true labor starts. The pediatrician can contribute expert postdelivery care to the premature infant, but this is not nearly as promising as the reduction of the loss of these babies by the avoidance of prematurity itself.

The second great cause of increased mortality in this group is hypoxia. This was certainly a critical factor in most of our stillborn babies. Enumeration of mortality statistics and causes of death does not reveal the entire picture in this regard. We have not been able to include the morbidity of the group in this series, which would be of great interest in itself. Besides the babies who were lost, there were those who suffered irreversible damage; others had atelectasis and hyaline membrane disease and survived only after a stormy, prolonged course in the nursery.

Premature separation of the placenta and placenta previa are prominent causes of fetal mortality in this group. The considerable loss of babies of preeclamptic and eclamptic mothers suggests that the state of the mother may well have had something to do with depressing the baby. There is no question but that a good regional anesthesia, limitation of heavy analgesia, avoidance of oxygen lack before and during the cesarean section, together with proper timing so as not to allow a long period of intrauterine hypoxia before the section is performed, are all important factors in reducing the fetal loss in this group.

The pediatrician can help immeasurably by recognizing the true nature of the problem. Lavage of the stomach, gentle handling, expert resuscitation, a patent airway, and the delivery of oxygen into the infant's lungs by the least traumatic means possible will all increase the salvage of the jeopardized babies.

Summary and Conclusions

Examination of infant mortality associated with deliveries by cesarean section over the last 48-year period at the University of California Hospital revealed that 569 sections were performed, with a total of 47 fetal deaths and a gross perinatal mortality of 8.2%. Allowance for congenital anomalies incompatible with life, known nonviable babies, erythroblastotic infants, and infants who were known to have died in utero before or during the operation corrects the mortality to 2.9%.

Detailed review of causes of death for the 16-year period from 1940 through 1955 revealed that prematurity is the largest single contributory factor to the high mortality rate. Fetal hypoxia, due to interference with placental circulation, and the toxic state of the mother are other leading causes of death and morbidity. While appraisal of the woman's arrival at term is difficult, this decision is extremely important so that a premature baby will not be delivered by an ineptly timed, purely elective section. On the other hand, where an obstetric emergency produces a critical intrauterine oxygen deficiency, rapid delivery, often by cesarean section, is equally important in augmenting fetal salvage.

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Treatment of Obesity.—There was a considerable increase in weight loss in most of the patients receiving the Biphetamine capsule medication. . . . Over 70% of the patients taking Biphetamine lost three to four pounds and more in the three week interval, in contrast to about 85% of the patients previously on amphetamine tablets who lost less than three to four pounds during three weeks of therapy. In addition to the superior effect of the Biphetamine, this single dosage form of medication was more convenient than tablet therapy. It avoided the accidental failure to take a tablet or the unconscious avoidance of it. However, most patients will take a capsule in the morning, since their intentions are usually good at this time, and thereafter they are released from the responsibility of the need to take further medication. In addition, the therapeutic effect is smoother because of the elimination of the sharp rises and declines in blood levels, and it is thus more effective in alleviating hunger. . . . Suppression of appetite and loss of weight after administration of one capsule of this material are superior to the results obtained with an even greater dose of amphetamine in tablet form. Side-reactions with the amphetamine-resin complex are somewhat less than with tablet therapy. . . . . The amphetamine-resin complex fulfills a need for a product which releases the drug on a predictable basis for a period of 10 to 14 hours.—S. C. Freed, M.D., J. W. Keating, B.S., and E. E. Hays, Ph.D., Amphetamine-Resin Complex for Prolonged Appetite Suppression, *Annals of Internal Medicine*, June, 1958.

DIAGNOSIS AND TREATMENT OF EOSINOPHILIC GRANULOMA OF SKULL

Robert S. Knighton, M.D.
and
J. DeWitt Fox, M.D., Detroit

• *The diagnosis of eosinophilic granuloma of bone was made in five cases here reported; in each there was a circumscribed area of swelling or tenderness on a cranial bone, a characteristic circumscribed lytic lesion in the roentgenograms, and confirmation by microscopic examination of tissue obtained at operation. Headache attributable to extension of the tumor along meningeal blood vessels was severe in one case and present in two others; the intracranial pressure was normal and the neurological findings were negative in all cases. Surgical removal and subsequent irradiation to a total of 600 to 2,000 r in air was followed by healing and complete relief of symptoms. Eosinophilic granuloma should be considered as a diagnostic possibility whenever a patient presents a localized tenderness of the scalp or a lytic lesion of the skull.*

Eosinophilic granuloma of bone should be considered in the differential diagnosis of lytic lesions of the skull. First described as a clinical entity in 1940 by Otani and Ehrlich [1] and independently by Lichtenstein and Jaffe,[2] eosinophilic granuloma of bone has been the subject of increasing interest and controversy. Various authors feel that these solitary destructive lesions of the table of the skull are local evidence of a more generalized disease process. In 1942, Green and Farber [3] studied 10 cases and concluded that lipid histiocytosis of cholesterol type (Hand-Schüller-Christian disease), Letterer-Siwe's disease, and eosinophilic granuloma of bone were clinical expressions of the same basic disorder. Later, in 1944, Jaffe and Lichtenstein [4] advanced a similar thought but differed on

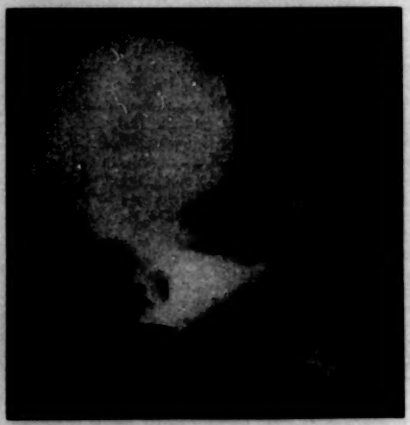

Fig. 1 (case 1).—Roentgenogram showing lytic lesion lying directly over branch of middle meningeal artery, which explains the symptoms of headache in this case.

etiology. In 1953, Lichtenstein [5] lumped these all under the single entity histiocytosis X. However, Otani and Ehrlich [1] felt that eosinophilic granuloma of bone, especially of the skull, should be classified separately from lipid histiocytosis of cholesterol type and Letterer-Siwe's disease, which carry a more serious prognosis and are of a more generalized nature. Eosinophilic granuloma of bone is primarily a disease of the reticuloendothelial system. At present, it is thought by some observers [6] to be infectious in nature, although no specific organism has been isolated.

From the Department of Neurological Surgery, Henry Ford Hospital.

Even as the controversy has arisen regarding the nature of this disease, so also have opinions differed on its treatment. Shuster and Flynn [6] favor surgical excision of the skull lesions, since drainage can be established if necessary. Gross and Savitsky [7] advise surgical excision in place of needle biopsy, since it provides a specimen for microscopic study and obviates roentgen therapy. Swain and Williams [8] describe perhaps the largest single skull lesion on record, which ended fatally but responded somewhat to surgery and roentgen therapy for a time. McCreary [9] records skin and bone involvement in a 2-year-old patient, with successful treatment with curettage of the bone and irradiation of the skin lesion. Curtis and Cawley [10] report multiple bone and skin lesions diagnosed by biopsy and clearing after irradiation. McCullough [11] claims good response to irradiation therapy of a skull lesion. He feels that this response supports the benign nature of this disease.

In the cases reported here, we wish to present the results achieved by combined surgical biopsy and roentgen therapy. The advantage of this plan of treatment is that it provides an adequate specimen for accurate microscopic diagnosis with the minimum of bone removal from the cranium. The roentgen therapy is followed by rather prompt regeneration of bone at the lesion site. The smaller the surgical lesion, the more rapidly this healing will occur. Since all of these cases consisted of solitary skull lesions that cleared remarkably after roentgen therapy, we, too, consider eosinophilic granuloma lesions of this character to be benign. However, we recognize that multiple lesions do occur. In these cases, the treatment is the same—surgical biopsy followed by irradiation. Sieracki [12] is also inclined to consider eosinophilic granuloma localized to bone as benign. It represents the successful confinement of the etiological agent.

Diagnosis

The history of onset of eosinophilic granuloma of bone is usually insidious. The patient may notice a tender spot on the scalp. His attention may be directed to it by a recent trauma to the skull, which may prompt a routine skull film. This may immediately disclose the lytic lesion. Clinically, however, the area may be swollen, with localized tenderness. On the other hand, the swelling may be painless. At times, the lesion may appear so rapidly and break through the outer table of the skull so quickly as to simulate a primary malignant tumor such as a sarcoma. The solitary lesion of the skull is the most common manifestation of the localized type of eosinophilic granuloma of bone. When multiple foci are present, other bones are involved in the following order of frequency: ribs, skull, femur, vertebrae, pelvis, mandible, and humerus.

The disease is most common in children and adolescents but has been reported in infants, young adults, and even middle-aged patients. Headache is sometimes a prominent symptom. This is especially true if blood vessels of the scalp or the dura mater are involved. In one of our patients (case 1) headache was severe due to invasion of the temporal bone, dura mater, and a branch of the middle meningeal artery. When a biopsy specimen of this lesion was examined, it was found to surround the artery and to be invading the dura mater. After its removal, together with a small segment of the dural branch of the artery, the headache disappeared. Blood-vessel involvement appears to be one cause of headache or localized tenderness of the scalp in these patients.

Neurological examination in our patients was negative. In none of these did the solitary, localized lesion produce any signs of increased intracranial pressure. Roentgenograms of the skull show a sharply circumscribed bone defect with geographical outline. The margins are well defined without surrounding sclerosis. Both tables are usually equally involved. Positive diagnosis must be withheld, however, until the surgical biopsy specimen has been examined microscopically. Microscopic examination reveals a loose stroma of reticular tissue with bone spicules and numerous eosinophils, leukocytes, and small lymphocytes with occasional multinucleated giant cells. No malignant change is seen. The following five case reports are illustrative of the therapy with combined biopsy and irradiation.

Report of Cases

Case 1.—The patient was a 38-year-old woman with a three-month history of left temporal headache, not throbbing in character, relieved by acetysalicylic acid (aspirin). There was no definite hemicrania or familial history of migraine. Neurological examination was essentially negative except for the finding of a small localized prominence over the left temporal region measuring about 1.5 cm. in diameter. There was no evidence of inflammatory change in the temporal artery on the affected side or the opposite side. Laboratory studies of the blood, urine, and serum were normal. Roentgenograms of the skull showed a lytic lesion over the left temporal bone about the size of a dime (fig 1). Chest films were normal. On Jan. 6, 1950, a biopsy specimen was taken from the left temporal bone lesion. This revealed eosinophilic granuloma that infiltrated the underlying dura mater and involved a branch of the middle meningeal artery. This area was clipped and the overlying granuloma removed and the bone curetted. Microscopic examination revealed eosinophilic granuloma that had involved the adventitial layer of the middle meningeal artery (fig. 2). There was also infiltration of the tumor into the area of the temporalis muscle. There were many large mononuclear cells and eosinophils in the adventitial areas of the small arteries. Sections of the tissue proper revealed many eosinophils, large mononuclear cells, and giant cells that appeared to be multinucleated. The patient received roentgen therapy immediately and was given 200 kv. of

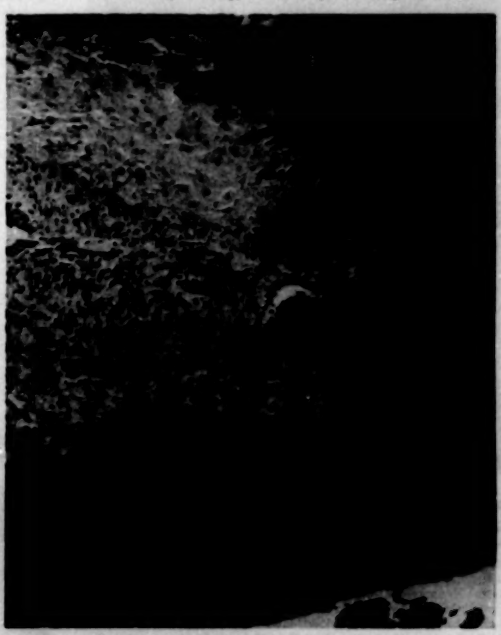

Fig. 2 (case 1).—Photomicrograph showing branch of middle meningeal artery. The eosinophilic granuloma surrounds the vessel but does not appear to invade the vessel wall (x 90).

irradiation weekly to a total of 600 r in air. Her headache was completely relieved after the biopsy and clipping of the middle meningeal artery branch. There was gradual regeneration of bone after roentgen therapy. The patient has been seen in our outpatient department and had not had any recurrence after six months.

Case 2.—The patient was a 6-year-old boy, first seen on Jan. 20, 1952, because of a swelling of the left eye of four months' duration. He had no visual disturbance and no pain. Neurological examination revealed an apparently normal 6-year-old boy, with no visual-field, funduscopic, or neurological abnormalities. Laboratory studies of the peripheral blood, urine, serum, and bone marrow were normal. Roentgenograms of the skull revealed an oval 1.5 by 1 cm. zone of destruction in the upper outer corner of the left superior orbital ridge. Chest films were normal. On Feb. 6, 1952, biopsy of the skull lesion revealed eosinophilic granuloma. A large amount of soft grayish tissue and periosteum was found. This was curetted for diagnosis. Microscopic examination showed the tissue to contain a con-

glomerate mixture of fibroblasts, epithelial cells, multinucleated giant cells, a few foamy histocytes, and a large number of eosinophils. The eosinophils were most prominent in the periphery of the lesion. The patient was given roentgen therapy of 100 r for six doses—a total of 600 r in air. After this there was a regression of the lesion and a gradual healing of the bone. Progress roentgenograms of the skull were essentially normal on Aug. 9, 1952, six months after treatment, and no recurrence was noted after four years of follow-up.

Case 3.—The patient was a 32-year-old right-handed man who gave a history of headache for three months after he received a bump on the head while at work. There was no loss of consciousness, no bleeding, and no swelling, but the area

Fig. 3 (case 3).—A, roentgenogram of skull before biopsy or radiation therapy. B, roentgenogram of skull taken after radiation therapy with 1,000 r in air. Note complete healing of lesion in left parietal area. Film was taken two years after therapy and shows no signs of recurrence.

struck, in the left parietal bone, continued to give pain. There was an associated frontal headache, dull and throbbing in character. Neurological examination was essentially negative except for slight tenderness over the left parietal area of the skull. Laboratory studies of the blood, urine, and serum were normal. A lumbar puncture was normal, with opening pressure 150 mm. H_2O. The cerebrospinal fluid was clear and colorless. The spinal fluid level of protein was 36 mg. and of sugar 72 mg. per 100 cc. The results of the Wassermann test were negative. An electroencephalogram and chest films were normal. Roentgenograms of the skull showed a 2-cm. rounded defect in the left temporoparietal area (fig. 3A.) On March 21, 1953, a surgical biopsy of the skull lesion was performed. This revealed eosinophilic granuloma. Microscopic examination showed a striking number of eosinophils intermixed with leukocytes and macrophages, scattered through a loose stroma of reticulated background (fig. 4 and 5). Bone spicules were present and showed marked scalloping, probably an index of the increased osteoclastic activity with very prominent cement lines seen in other bone spicules. No malignant change was noted. The patient was given roentgen therapy consisting of 100 r for nine doses and 200 r as a final dose, with a total of 1,000 r in air. Repeat roentgenograms of the skull taken July 11, 1953, showed evidence of healing in the left parietal bone (fig. 3B). Subsequent films, taken July 26, 1955, more than two years later, showed no evidence of the skull lesion and no recurrence elsewhere.

Case 4.—The patient was a 14-year-old right-handed boy who was in a fight on April 10, 1955. He suffered a blow to the left side of the head and was quite dizzy afterward. After this, he noticed a tender area in the left parietal region of his skull. Physical and neurological examination was negative. Laboratory studies of his blood, urine, serum, and blood chemistry were normal. A roentgenogram of the skull showed a radiolucent area in the left parietal region 2.5 cm. in diameter (fig. 6A). A chest film was normal. On May 18, 1955, biopsy and curettage of the lesion were performed. At operation the frozen section and imprint smear revealed eosinophilic granuloma, later confirmed on section. The lesion, measuring 2.5 cm. in diameter, was curetted up to the bony edge. Microscopic examination showed sections consisting of eosinophilic granuloma of the skull. These are composed of masses of cells set in a somewhat fibrous stroma. There were numerous eosinophils and a large number of nuclear cells. Occasional multinucleated giant cells were encountered. The remaining cellular structures were small lymphocytes, occurring in fairly large clumps. After biopsy and confirmation of the diagnosis by pathological section, the patient was given a series of two courses of radiation therapy, each consisting of 200 r at 10 different sittings. A total of 1,000 r in air was given over the left parietal area, and another course of 1,000 r in air was given in 200-r doses over the occipital area to a small second lesion. The patient has been free of any symptoms since irradiation, with no further head or skull pain. He has regrowth of bone in the former skull defect, as shown on the latest roentgenograms of the skull, taken one year later (fig. 6B). At follow-up, one year after treatment, no recurrence was noted.

Case 5.—The patient was a 32-year-old right-handed female with a history of right supraorbital headache of one month's duration. She had occasional dizziness and a tender area over

Fig. 4 (case 3).—Photomicrograph of eosinophilic granuloma showing loosely textured connective tissue stroma in which there are numerous eosinophils, giant cells, and histiocytes (×710).

the right temporal area of the skull. Neurological examination was essentially negative except for the 2.5-cm. tender swelling in the right temporal area. Laboratory studies of the peripheral blood, urine, and serum were normal. Roentgenograms of the skull showed an irregular 1 by 1 cm. radiolucent area in the right frontal bone. A chest film was normal. On Oct. 23, 1954, a surgical biopsy was made of the skull lesion. A vascular and reddish purple lesion was curetted from the bone. The tumor extended through the inner and outer tables of the skull, but the dura mater was not involved. Microscopic examination revealed eosinophilic granuloma. The tumor was composed of eosinophils, with occasional neutrophils and plasma cells in a

loose reticular stroma. The patient was given a total of 800 r in air. Her headaches and pain in the temporal region completely subsided, and she had no evidence of recurrence after 18 months. Repeat roentgenograms of the skull on July 26, 1955, showed no evidence of the previous lesion in the right frontal bone.

Comment

The diagnosis of eosinophilic granuloma of the skull often rests with the family physician or specialist who first sees the patient and suspects a lytic lesion. In any case of persistent localized tenderness of the scalp or localized headache, roentgenograms of the skull should be taken. This will almost invariably localize the lytic lesion and determine its size. The final diagnosis, of course, is a microscopic one after biopsy. In view of the unknown etiology of this lesion, no ironclad formula for its handling can be laid down. However, because it behaves in a benign fashion, as compared with Letterer-Siwe's disease and lipid histiocytosis of cholesterol type, it is deemed safe to handle it as a benign lesion. The cases presented tend to support this view. They were treated by surgical biopsy and irradiation, with immediate regression of the skull lesions. In the follow-up period, ranging from one to four years, no recurrence has been noted. However, should recurrence occur in later study, more radical therapy might be necessary. Until such time, it seems best to treat these lesions as outlined, i. e., by surgical biopsy and irradiation.

Fig. 5 (case 5).—Photomicrograph of eosinophilic granuloma showing junction of fibrous tissue and tumor (× 150).

Summary

Since 1952, we have seen five cases of eosinophilic granuloma of the skull. It is important to consider the possibility that this disease exists when there is any localized tenderness of the scalp or any lytic lesion of the skull. Since eosinophilic granuloma of the skull is frequently solitary and benign and carries a good prognosis, accurate diagnosis should be made by surgical biopsy, with removal of a specimen large enough for microscopic examination. The treatment is uniformly successful with roentgen therapy. Usually, a course of six exposures of 200 r in air is sufficient. The patient's scalp pain is relieved immediately after biopsy and irradiation. The regrowth of the bone of the cranium is usually demonstrated roentgenographically within six months.

2799 W. Grand Blvd. (2) (Dr. Fox).

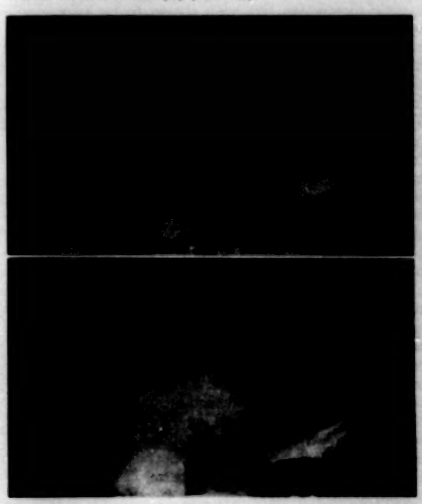

Fig. 6 (case 4).—*A*, roentgenogram of skull taken before therapy showing large lytic lesion in left temporoparietal area measuring 2.5 cm. in diameter. *B*, roentgenogram of skull taken one year after surgical biopsy and irradiation therapy with 1,000 r in air to lesion and a second course of 1,000 r in air to the occipital area for second lesion. Note almost complete healing of the lytic lesion and no evidence of recurrence.

Dr. Joseph E. Sieracki of the Department of Pathology, Henry Ford Hospital, procured and described the microscopic sections.

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ISOLATION OF ECHO VIRUS TYPE 6 DURING OUTBREAK OF SEASONAL ASEPTIC MENINGITIS

David T. Karzon, M.D., Almen L. Barron, Ph.D., Warren Winkelstein Jr., M.D.
and
Seymour Cohen, M.D., Buffalo

• *Symptoms of aseptic meningitis occurred in 17 children and in 7 young adults out of 500 inhabitants of a village in July, 1955. Seven boys were hospitalized, and all had fever, headache, signs of meningeal irritation, and gastrointestinal complaints. Pain, lethargy, mild muscular weakness, and altered reflexes were present in some cases. Improvement was rapid, and all patients were discharged well, within 3 to 10 days, with no residual findings except occasional slight muscular weaknesses and minimal hamstring spasm. Laboratory observations included detailed virus studies of the cerebrospinal fluid, blood, throat swabs, and fecal specimens. No rise of poliovirus neutralizing antibody was demonstrable in any of the patients, but in all there were rises in circulating antibody to ECHO (enteric cytopathogenic human orphan) type 6 virus. Specific antibody appeared on the fifth day of illness and was still present after seven months, when the only residual finding was absence of the abdominal reflexes in two patients. The virus was isolated, and evidence of its etiological role is given. The disease could not be distinguished clinically from preparalytic poliomyelitis when the patients were admitted to the hospital. There are indications that epidemics of this kind are not unusual or isolated occurrences.*

The clinical syndrome termed nonparalytic poliomyelitis, often referred to by the more general term aseptic meningitis, has been shown to be associated with poliovirus as well as with the Coxsackie viruses of group B. Furthermore, a variety of "enteric viruses" has recently been isolated from the human intestinal tract, and isolations of such viruses have been reported from the stools of patients with aseptic meningitis.[1] These new agents, referred to as orphan viruses, have proved to be serologically and biologically distinct from both the poliovirus and Coxsackie groups.[2] Certain orphan viruses have been recently classified as the ECHO viruses (enteric cytopathogenic human orphans), of which 13 serotypes have been identified and characterized.[3] These enteric viruses appear to be widespread during the summer season in the normal population.[4] Despite the frequency with which they have been isolated, evidence for specific causal relationship between the ECHO viruses and any disease entity has been scanty. The present study reports an outbreak during the summer of aseptic meningitis resembling nonparalytic poliomyelitis in a small community in western New York (Holland, N. Y.) and describes the clinical syndrome in some detail. A total of 14 agents, all identified as ECHO virus type 6, were recovered from 7 hospitalized individuals, 13 household associates, and 3 nonhospitalized patients. Evidence is presented that the agent was etiologically related to the clinical illness.

Epidemiology

Seven patients were admitted to the Buffalo Children's Hospital from the village of Holland, population 500, with a diagnosis of nonparalytic poliomyelitis, between July 5 and July 21, 1955. Three of these patients were from one family, two from a second, and one each from a third and fourth. This aggregation of cases without paralysis, with an unusual family concentration in a small rural community, warranted further investigation. In addition to these seven patients, 17 nonhospitalized patients were seen by the local physician. During July, August, and September, 1955, an outbreak of aseptic meningitis was generalized in western New York. It will be the subject of a subsequent communication.

Approximately three-fourths of the cases in Holland (17 of 24) occurred in persons between the ages of 5 and 14 years, and the remainder were in young adults. While there were twice as many males affected as females (16 males, 8 females), this may not be significant in view of the small number of cases. The epidemic extended for a period of approximately one month. The dates of onset occurred continuously over this period, suggesting that the disease was disseminated through contact rather than by a common source. There was a marked familial aggregation of cases. The 24 cases occurred in 16 households, with 10 households having a single case, 4 households two cases, and 2 households three cases each. The over-all community attack rate was 4.8 per 100 persons, while the secondary attack rate among the 67 household contacts of the 16 patients with primary cases was 12 per 100 persons.

Clinical Description of Hospitalized Patients

Seven boys, varying in age from 4 to 17 years, were hospitalized at the Children's Hospital in Buffalo (table 1). The cardinal symptoms at the onset were fever, headache, gastrointestinal complaints, and poorly defined pains in the abdomen or chest or generalized muscular pains. The important findings on examination in the hospital were evidence of meningeal irritation in all cases and, in some cases, mild reflex changes, transitory muscle weakness, and pharyngeal injection. The total duration of illness varied from 5 to 14 days, averaging 9 days.

From the Department of Pediatrics and the Statler Research Laboratories of the Children's Hospital; the Department of Bacteriology and Immunology, University of Buffalo School of Medicine; and the Erie County Health Department.

Fever.—All seven patients had fever, with the duration varying from three to six days and averaging four days. The highest recorded temperatures in the hospital varied from 100.4 to 102.6 F (38 to 39.2 C).

Headache.—All patients complained of severe headache. It was the prominent presenting complaint and the main reason for seeking a physician's advice. Six patients had a characteristically frontal headache. Two of these complained of retrobulbar localization. Headache was generalized in one patient.

Gastrointestinal Complaints.—All patients had symptoms referrable to the gastrointestinal tract; six had nausea and vomiting, and one each had diarrhea and constipation.

Pain.—Ill-defined pain occurred in the epigastric or periumbilical areas of the abdomen in five patients, mild chest pain in two, and generalized limb and back pain in one.

Meningeal Irritation.—On examination, all patients showed mild to moderate stiffness of the neck and back and spasm of the hamstring muscles.

Neuromuscular Changes.—Three patients showed some muscle weakness rated as "poor" to "fair" on examination by a physiotherapist at the time of discharge from the hospital, when the temperature had been normal for several days. One patient had mild weakness of the anterior and posterior neck muscles and of the upper and lower groups of the back and slight weakness of the gluteus maximus bilaterally. Two patients had slight weakness of the anterior neck muscles only. At an examination seven months later, no muscle weakness, atrophy, or spasm persisted in any of the patients. In the acute phase, four individuals were found to have depressed superficial or deep tendon reflexes. After seven months, the abdominal reflexes remained absent in two patients.

Pharyngeal Injection.—In three of the seven patients there was injection of the soft palate that extended in rim-like fashion down the anterior pillars. A fourth patient had a diffuse erythematous pharyngitis with a small amount of white exudate on one tonsil.

Clinical Laboratory Findings

All seven patients had abnormal cerebrospinal fluid findings. The fluid was grossly clear, but from 33 to 231 cells per cubic millimeter were present, of which 65 to 95% were lymphocytes. The total protein content varied from 22 to 98 mg. per 100 cc. Four patients had a level of 40 mg. per 100 cc. or greater. The cerebrospinal fluid glucose levels were within normal range. All spinal fluid cultures were sterile on bacteriological examination. The peripheral blood showed a normal or slightly elevated white blood cell count, with a slight increase in the neutrophil series.

Course

The headache, lethargy, anorexia, vomiting, and fever present on admission to the hospital subsided rapidly in all patients. The children were usually free of discomfort and eating well within 24 to 48 hours. Stiffness of the neck and back and hamstring spasm cleared very quickly, with much improvement in 24 hours and disappearance, with the exception of minimal hamstring spasm, by the time of discharge (after 3 to 10 days). Prone packs (moist heat), when used, were not required more than two days. Treatment was entirely symptomatic. Intravenous administration of fluids was not required, and no antibiotics were given. The case history of one individual is presented in detail.

Case 15.—A husky 17-year-old boy was well until July 4, 1955, when he developed a generalized headache, dull aching abdominal pain, sharp pains in the chest, and a temperature elevation to 101 F (38.3 C). The next day, despite increasing generalized muscle aches and severe headache, which had localized in the frontal region, he continued working in his usual summer employment at a foundry. The next day he remained in bed because of moderately severe hip and leg pains, generalized weakness, and transient episodes of dizziness. On July 7, the day of admission to the hospital, the patient noted retrobulbar pain and vomited once. The pains in the abdomen, hips, and legs had increased in severity. Stiffness of his neck appeared at this time. The patient was admitted to the Children's Hospital simultaneously with a younger brother (case 16) suffering from a similar illness. A second brother (case 11) had been admitted two days previously. A third brother remained well at home.

At time of admission, his temperature was 102.4 F (39.1 C), his respiration rate was 32 per minute, and his pulse rate was 90 per minute. The blood pressure was 120/60 mm. Hg. He was moderately and acutely ill. His neck and back were stiff and resistant to flexion. Moderate hamstring spasm was present.

Table 1.—*Incidence of Major Clinical Features in Seven Hospitalized Patients*

Clinical Feature	Patients
Fever	7
Headache	7
Signs of meningeal irritation	7
Gastrointestinal symptoms	7
Pain	6
Abdominal	5
Chest	2
Generalized muscular	1
Marked lethargy	7
Mild muscular weakness	3
Acute phase	3
Follow-up	0
Reflex changes	3
Pharyngeal injection	4

Motor power was normal. The superficial abdominal reflexes were absent in all quadrants. The left cremasteric reflex was absent and the right diminished. The deep tendon reflexes were normal on admission, but on the second hospital day there was a general depression of reflexes in both upper and lower extremities. By the next day, all deep tendon reflexes had returned except the right knee jerk. The temperature fell to normal within 24 hours of admission, and the patient was free of headache. Lumbar puncture on admission revealed an initial pressure of 168 mm. H_2O, with clear spinal fluid containing 231 white blood cells per cubic millimeter, 71% of which were lymphocytes. The total level of protein was 98 mg. and of glucose 92 mg. per 100 cc. Follow-up examination seven months after discharge revealed the continued absence of the abdominal and left cremasteric reflexes and somewhat diminished ankle and knee jerks in the right leg. The patient also complained of occasional back and chest pains and occipital headaches, with onset dating from the illness.

Virus Isolation

Methods.—From the seven hospitalized patients, throat swabs, spinal fluid, and blood specimens from the acute phase were obtained on admission. Fecal specimens were collected within 48 hours. Blood specimens from the convalescent phase were obtained on discharge from the hospital (five to nine days later) and seven months after hospitalization. Studies were car-

ried out on 13 healthy household associates of the 7 patients. Specimens were also collected from three nonhospitalized patients in the community.

Throat and rectal swabs were placed in tubes containing 2 ml. of tissue culture nutrient medium. Specimens were frozen either immediately at −20 C or after 24 hours' storage in a refrigerator. Stool specimens were prepared as 10 to 20% suspensions in tissue culture medium. The turbid stool suspensions and the throat and rectal swab eluates were clarified by centrifugation. Spinal fluids were used without treatment. For virus isolation, a 0.2-ml. aliquot from each specimen was inoculated into trypsin-dispersed monkey kidney monolayer tissue cultures (Melnick[19]) in 16-by-125-mm. test tubes. The cells were propagated in a growth medium consisting of 97.5% Hanks' balanced salt solution, 0.5% lactalbumin hydrolysate, and 2% calf serum, with 200 units of penicillin and 200 mcg. of streptomycin added per milliliter. At the time of inoculation, the growth medium was replaced with 0.9 ml. of maintenance medium consisting of Earle's saline solution, lactalbumin hydrolysate, and calf serum. Specimens were inoculated into each of three tissue cultures and the tubes incubated at 36 C.

Table 2.—*Recovery of Fourteen Cytopathogenic Agents in a Study of Aseptic Meningitis in Holland, N. Y.*

	Hospitalized Patients		Specimen*			Healthy Household Associates	
Family	Lab. No.	Age, Yr.	Stool	Throat	Cerebrospinal Fluid	No.	Agents Isolated
	11	6	+	+	−	3	2
1	15	17	+	−	−		
	16	11	+	−	−		
2	14	5	+	+	−	2	0
	17	5	+	−	−		
3	18	12	+	+	−	6	0
4	28	4	+	+	−	2	0

Totals	Stool	Rectal Swab	Throat	Cerebrospinal Fluid
7 hospitalized patients	7/7	N.D.*	4/7	0/7
13 healthy household associates	2/5	0/5	0/6	N.D.
3 nonhospitalized patients	1/3	N.D.	N.D.	N.D.

* + = positive; − = negative; N.D. = not done.

Microscopic observations for the appearance of viral cytopathogenic effect were made daily or every other day. Careful examination was made for evidence of cellular damage due to toxicity of the specimens. This was usually manifest within 24 hours. Stool inoculums were generally slightly toxic, while throat and rectal swabs were essentially nontoxic. Spinal fluids were also nontoxic and in fact appeared to have some nutritional value for the monkey kidney cells. Throat swabs and spinal fluids were considered negative at the end of a seven-to-nine-day incubation period unless there were changes in the kidney cells suggestive of viral effect, in which case the fluids were harvested and passaged a second time in tissue culture. Stool specimens or rectal swabs were considered negative only after two passages had been completed.

Identification of Agents Isolated.—The results of the virus isolation studies are tabulated in table 2. A total of 14 cytopathogenic agents were isolated. Virus was recovered from the stools of all seven hospitalized patients and from the throat swabs of four. No cytopathogenic agents were isolated from their spinal fluids. Two agents were recovered from stools of healthy household associates, while their other specimens were negative. One stool agent was recovered from a nonhospitalized patient. All 14 agents were examined in a tissue-culture neutralization test against prototypic poliomyelitis monkey antiserums. None of the 14 agents was neutralized by a mixture of the three types of poliomyelitis antiserums. It was therefore concluded that these agents were not poliovirus or a mixture of polioviruses.

Four stool agents (no. 11, 14, 18, and 28), from patients representing the four families studied, were examined in a virus neutralization test with Coxsackie prototypic antiserums of those types presently known to be cytopathogenic in tissue culture (types A9 and B1-5). None of these agents was neutralized by the above serums. In addition, the above four agents were inoculated into infant mice less than 24 hours old via the intraperitoneal route. There was no evidence of illness in the inoculated mice. In three instances, a second blind passage was made in infant mice with mouse brain–muscle suspensions; there was no apparent infection. Inoculation of the first-passage brain-muscle suspensions into tissue culture failed to demonstrate the presence of live virus and indicated a failure of the virus to survive through one passage in infant mice.

Since the Holland agents were not identifiable as poliomyelitis or Coxsackie viruses, according to both serologic and animal inoculation studies, they were designated at this point as orphan viruses. The following serologic studies were undertaken to elucidate the antigenic relationships of the 14 agents among themselves and to known ECHO virus types. Two of the fecal agents (no. 14 and 18) were selected for the preparation of specific antiserums. Rabbits were given 1 ml. of undiluted virus intravenously followed by five weekly doses of 1 ml. intramuscularly. Seven to 10 days after the last dose, the rabbits were exsanguinated by cardiac puncture. The antiserums thus prepared were capable of neutralizing 100 TCD_{50} of homologous virus in titers of 64 to 512. (All neutralization titers are expressed as reciprocals of the 50% serum dilution end-points.) All of the 14 orphan viruses were readily neutralized by either of the two Holland prototypic rabbit antiserums. It was thus apparent that the 14 orphan agents isolated in the Holland study were of the same serologic type.

In addition, the two Holland orphan strains were examined serologically with rabbit antiserums prepared against four other orphan viruses isolated from patients residing in other communities in western

New York who had had aseptic meningitis in 1955. Table 3 summarizes the results. It was found that the Holland agents were serologically related to two of the other four agents, one from Buffalo (no. 25) and the other from Springville, N. Y. (no. 8). The remaining two orphans from Batavia (no. 801) and Buffalo (no. 32) were found to be serologically alike but unrelated to the Holland group. For simplification,

TABLE 3.—*Serotyping of Orphan Viruses Isolated from Patients with Aseptic Meningitis*

Virus Neutralized (No.)	Antiserum: Holland, N. Y. 14	14	Other Isolations in Western N. Y. 25	8	32	801	Gamma Globulin
14*	+‡	+	+	+	−	−	+
14†	+	+	+	+	−	−	+
25*	+	+	+	+	−	−	+
8*	+	+	+	+	−	−	+
32†	−	−	−	−	+	+	+
801†	−	−	−	−	+	+	+
ECHO Type 6	+	+	N.D.§	N.D.	−	−	+

* BOP-1.
† BOP-2.
‡ N.D. = not done.
§ + = positive, − = negative.

the Holland agents and serologically related orphan viruses were designated tentatively as Buffalo orphan prototype–1 (BOP-1), and the second serotype, representing the two orphan agents from patients no. 801 and 32, was designated as BOP-2.

To determine relationship to presently known ECHO virus types, the 13 ECHO virus prototypes were examined in a virus neutralization test against BOP-1 and BOP-2 rabbit antiserums, with 100 TCD_{50} of each virus employed. ECHO virus type 6 was specifically neutralized by BOP-1 antiserum but not by BOP-2 antiserum. It was concluded that the 14 orphan viruses isolated from Holland patients with aseptic meningitis and their healthy family contacts, as well as two other orphan agents isolated from patients with aseptic meningitis, were serologically identical with the ECHO type 6 prototype. As has been noted in table 2, no viral agents were recovered from cerebrospinal fluid specimens from the seven Holland patients. However, during the investigation of the concurrent generalized outbreak of seasonal aseptic meningitis in western New York (July through September, 1955), a total of 10 orphan agents were recovered from cerebrospinal fluid specimens from hospitalized patients. Seven of these 10 agents have been found to be serologically identical with ECHO type 6.

Antibody Response in Patients

Poliovirus Antibody Studies.—The serums obtained during the acute and convalescent stages of the disease from the seven patients from Holland were studied for their circulating antibody to poliomyelitis. The antibody determinations were made by means of a metabolic inhibition test, with fourfold dilutions of serum used. During the course of illness, there was no demonstrable rise in poliovirus neutralizing antibody detected in any patient. It was concluded from the virus-isolation and serologic evidence that infection with any one type of poliovirus had not occurred during the period of illness.

ECHO Virus Type 6 Antibody Studies.—Antibody studies on the Holland patients' serums were carried out in a tissue-culture virus-neutralization test with ECHO virus type 6. Twofold dilutions of serum were tested against 100 TCD_{50} of ECHO virus type 6. Four tissue-culture tubes were employed per serum dilution. The 50% serum dilution end-point (Reed and Muench) was determined, based on readings made 48 hours after all virus control tubes showed definitive cytopathogenic effect. Table 4 summarizes the results obtained. The patients demonstrated rises in circulating antibody to ECHO type 6 virus in a characteristic manner. During the first three days of illness there was little or no demonstrable antibody. Between 5 and 12 days, circulating antibody to the virus appeared, although in modest titer. Seven months after infection, neutralizing antibody was still present. In view of the low order of neutralizing-antibody response, it was considered of interest to do determinations of the antibody content of human gamma globulin to ECHO virus type 6. Human gamma globulin was therefore employed in a neutralization test with one of the Holland agents (no. 14) and also with the prototype ECHO virus type 6. The antibody titers were 32 against each of the viruses. This titer is significant, although of low order.

Comment

Etiological relationship between a common endemic agent and a common clinical syndrome occurring simultaneously in a community is difficult to establish. Proof of such relationship must at the present time depend upon the demonstration of (*a*) association of

TABLE 4.—*Neutralizing Antibody Titer Versus ECHO Virus Type 6 in Seven Patients with Aseptic Meningitis in Holland, N. Y.*

Patient No.	Day of Disease: 1	2	3	4	5	6	7	8	9	10	11	12	7 Mo. Follow-Up
11			2.5				>64						48
14	<2				11								22
15			<2									9	4
16	<2									27			5
17	<2	<2								14			10
18			<2					27					27
28		<2					32						55

the agent with clinical cases, (*b*) recovery of the agent from a parenteral site of disease (e. g., cerebrospinal fluid), (*c*) specific neutralizing antibody response during the course of illness, and (*d*) corollary epidemiological evidence within a localized outbreak.

The need for careful evaluation of the role of the orphan viruses in disease is emphasized by the fact that orphan viruses have already been demonstrated to be worldwide in distribution and highly prevalent

during the summer months. They have been isolated from fecal material from many areas in the United States[5] and also in Egypt,[14] the Philippine Islands,[5] Canada,[6] and Sweden.[15] Two recent surveys have shown that orphan viruses may be common enteric inhabitants. In one survey undertaken by Ramos-Alvarez and Sabin, of 1,566 healthy children in Ohio in the summer of 1953, 25 orphan viruses were recovered from the stools, or an over-all rate of 1.6%.[16] In the group with the highest recovery rate, namely, children under 10 years of age who came to clinics from families with low income, the recovery rate was approximately 6%. These isolations fell into at least three serotypes. In a three-year survey of a healthy population of children in West Virginia, orphan viruses were recovered by Honig, Melnick, and coworkers in 33 instances from 1,558 stool specimens, a rate of 2.1%.[16] The highest recovery rate, 11.2%, was from a low socioeconomic area in the four-month period from July through October.

The present demonstration of 7 ECHO 6 viruses among 10 orphan agents recovered from the spinal fluids of patients with aseptic meningitis in western New York is indicative of the invasive properties of this virus. Duncan, Rhodes, and others[16] recovered two orphan agents, type unidentified, from the spinal fluids of patients with aseptic meningitis. Steigman, Kokko, and Silverberg isolated an orphan agent from the spinal cord of a child with a fatal infection that clinically and pathologically resembled bulbo-spinal poliomyelitis.[7] This agent has recently been identified serologically as ECHO virus type 2.[9] Further attempts to isolate and identify ECHO virus from spinal fluid and nervous tissue will be helpful in establishing the full range of the clinical central nervous system syndromes produced by ECHO viruses.

The Holland patients' neuralizing antibody response, although of a modest order, is in keeping with the low level of antibody for ECHO 6 found in pooled human gamma globulin. This may suggest that under natural conditions of infection the ECHO 6 virus is a poor antigen. However, the absolute level, dependent as it is upon the technique of mensuration, may simply reflect an artefact of the methods employed. With use of an analogous technique, neutralizing antibody titers against poliovirus are approximately tenfold to fiftyfold higher. If one assumes that the pooled gamma globulin represents an approximate twenty-fold concentration of antibody, one can presume that the rather low titer of 32 suggests either a small number of adults with sustained high titers of antibody in the population or perhaps a larger number of adults with a barely detectable neutralizing titer. The serologic experience of the population is under study. Utilization of a rise in neutralizing antibody as a diagnostic tool appears to be feasible in this disease, since serum taken prior to the fifth day of disease will in general fail to show antibody and that taken after the fifth day will demonstrate a rise. This is in contrast to the serodiagnosis of poliomyelitis, where the neutralizing antibody has, in the majority of cases, attained maximal titer at the time of recognition of the disease and hospitalization.

The clinical course of illness of the Holland cases was typical of the syndrome known as aseptic meningitis. On admission, symptoms and signs of the patients could not be distinguished on clinical grounds from those of preparalytic poliomyelitis. In retrospect, several features distinguished the Holland cases of aseptic meningitis. First was the apparent high familial incidence of this illness as compared to that usually seen in poliomyelitis. As a corollary, the percentage of manifest versus inapparent disease appeared to be higher than in poliomyelitis. Second, it was noticeable that hot moist packs to the back (prone packs) were not required for more than two or three days, indicating the rapid subsidence of back and hamstring spasm. The significance of the mild muscle weakness and depressed deep tendon and superficial reflexes could not be properly assessed because of lack of controls.

There are already several indications that the association of ECHO virus type 6 with a localized outbreak of cases of aseptic meningitis as occurred in Holland may not be an unusual or isolated occurrence. Studies of a large epidemic of aseptic meningitis in all of western New York in 1955 indicate that such an association was widespread. Simultaneously, at the other end of the state, in Troy, an epidemic of presumably the same illness was studied by Dalldorf.[9] Many strains serologically identical with ECHO virus type 6 were isolated from patients' stools. An outbreak of nonparalytic poliomyelitis in Massachusetts during the summer of 1954 was recently described by Kibrick and others.[10] A high recovery rate of orphan viruses, largely ECHO virus type 6, was made from patients with this illness.

Summary

An outbreak of aseptic meningitis, involving 24 cases, including seven hospitalized children, occurred in Holland, N. Y., population 500, in July, 1955. The predominant clinical symptoms and signs included fever, frontal headache, signs of meningeal irritation, nausea and vomiting, generalized vague pains, minimal transitory muscle weakness, depression of superficial and deep tendon reflexes, and pharyngeal injection. All patients had a pleocytosis, predominantly lymphocytic. ECHO virus type 6 was isolated from 7 stools and 4 pharyngeal specimens of 7 hospitalized children, from 2 of 10 stools and none of 6 pharyngeal specimens of 13 healthy household associates, and from 1 of 3 stools of 3 nonhospitalized patients. All seven hospitalized patients developed a neutralizing antibody response to ECHO virus type 6 beginning on the fifth day of illness. The antibody was still present after seven months. Pooled human gamma globulin had a neutralizing antibody titer of 32 against this agent. In addition, 10 orphan agents were isolated from the spinal fluids of patients in other communities during the course of a subsequent generalized outbreak of seasonal aseptic meningitis in western New York. Seven of these agents were identified as ECHO virus type 6. The high virus recovery rate from stool and pharynx, the epidemiological data, the neutralizing antibody response during the course of illness, and the demonstration of virus

in the spinal fluid of patients are presented as evidence for establishing an etiological role for ECHO virus type 6 in seasonal aseptic meningitis.

Addendum

Since this paper was submitted for publication, Davis and Melnick [11] have reported 24 cases of aseptic meningitis associated with recovery of ECHO virus type 6.

This study was aided in part by contracts with the Communicable Disease Center, U. S. Public Health Service, Atlanta, Ga., and the Erie County (N. Y.) Laboratory.

The prototypic poliomyelitis monkey antiserum used in this study was supplied by Dr. Herbert Wenner, University of Kansas, Kansas City. The Coxsackie prototypic antiserum was supplied by Dr. Gilbert Dalldorf and Miss Grace Sickles, New York State Department of Health, Albany. The 13 ECHC virus prototypes were supplied by the Committee on ECHO Viruses. The human gamma globulin a 16.5% concentration without preservative, was supplied as C-262 by Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

Drs. Clinton Strong, Holland, N. Y., and A. Wilmot Jacobsen, Buffalo, made available clinical data on their patients for this study.

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METHYLPHENIDATE (RITALIN) HYDROCHLORIDE PARENTERAL SOLUTION

PRELIMINARY REPORT

John T. Ferguson, M.D., Frank V. Z. Linn, M.D., John A. Sheets Jr., M.D.
and
Mervyn M. Nickels, M.D., Traverse City, Mich.

Methylphenidate hydrochloride was administered in 10-mg. doses by intravenous injection to 164 hospitalized mental patients who manifested sleepiness and other symptoms of overdosage with tranquilizing drugs. The conditions of only 4 of the 164 were refractory to the analeptic effects of the methyphenidate; the other 160 all responded to one, two, or at most three injections by increase in alertness and decrease in side-reactions. Safe and effective dosages were thus determined, and in addition it was found that the improved condition of 151 of the 160 patients could be maintained by giving the methylphenidate solution thrice daily by mouth. A group of 11 chronic, regressed, underactive patients were then treated with intravenous injections of the drug. Three injections of 10 mg. sufficed in every case to cause marked clinical improvement, with increased activity, sudden awareness of surroundings, and other marked changes of behavior. These changes were obtained repeatedly, appeared promptly, were of limited duration, and were not seen after injections of a placebo. They are exemplified in the case histories of two patients who, after 21 and 17 years of extreme inactivity in the hospital, showed dramatic improvement in behavior.

The psychoanaleptic activity, or stimulating activity on the central nervous system, of orally administered methylphenidate (Ritalin) hydrochloride is well documented clinically.[1] However, clinical information concerning this drug in a new form, methylphenidate (Ritalin) parenteral solution (1%), is needed. This report, although covering our observations made during approximately six months of intravenous administration of this solution to 164 hospitalized mental patients, has been prepared primarily as a preliminary report of findings observed when this solution was administered to 11 chronically regressed, negative, and underactive patients who had been hospitalized for an average of 16 years.

Effects of Drug

In our preliminary evaluation of methylphenidate parenteral solution, we first administered the drug intravenously to patients demonstrating sleepiness, lethargy, tremors, drooling, nasal congestion, conjunctivitis, and Parkinson-like gait produced by too much reserpine, promazine, or chlorpromazine hydrochloride. One hundred six of the 164 patients who received 10 mg. (1 cc.) of the solution intravenously demonstrated improvement of their mental alertness and a

From the Traverse City State Hospital.

decrease in their side-reactions within 5 to 90 minutes after the injection. Thirty-eight of the 164 responded only after a second intravenous injection of 10 mg. was administered, and 16 of the remaining 20 required 30 mg. intravenously before a clinical change was recorded. The remaining 4 of the 164 showed no change, even though their dosage was raised to 90 mg. intravenously.

After administering 10 to 30 mg. intravenously, as individually needed, three times daily for periods ranging from 24 to 72 hours (three to nine injections), we have been able to maintain the improved condition of 151 of the 160 patients with a comparable dose of methylphenidate given orally three times a day. During the period that the methylphenidate solution was administered intravenously, we recorded no gross change in blood pressure, pulse, or respiration for 160 of the 164 patients. Eight of the 164 became apprehensive and fearful after two to four injections, and 8 others became overactive. These symptoms were alleviated when the dosage was decreased. There was no evidence of serious changes of the skin or tissues at the site of injection, even when extravasation occurred on a few occasions; also there was no evidence of phlebitis. Thus it is indicated that this parenteral solution seems to be well tolerated locally as well as systemically.

From the 164 patients we had acquired a knowledge of indication for use of the drug as well as the proper dosage, safety, and activity of the drug. This prompted us to try a course of therapy with methylphenidate parenteral solution on a group of chronically regressed, underactive patients. Our basic requirements for the patients were simple: a long history of underactivity, no visible reaction when a towel or other object was tossed toward them, and a behavior pattern that indicated they needed help in executing routine daily tasks. Eleven such patients were chosen from another service. An initial intravenous injection of 10 mg. of methylphenidate parenteral solution produced no clinical change in the 11 patients. However, after the second 10-mg. injection and more noticeably after the third intravenous injection of 10 mg. was administered, there was marked clinical improvement in all 11 patients—within minutes. To illustrate the type of patient in this special study and to give examples of our method of administering the solution, two cases are presented.

Report of Cases

Case 1.—A 44-year-old male had been admitted to the Traverse City State Hospital in 1935. He never talked, even when prodded. During the 21 years of his hospitalization he spent practically every waking hour sitting in a chair in the same corner of the same ward without moving. He had to be started to meals, told to go, and helped at the toilet. He needed help in dressing and undressing. He made no visible reaction when a towel was repeatedly thrown to him. At 2:50 p.m. on Sept. 5, 1956, he was given 10 mg. of methylphenidate parenteral solution intravenously. He showed little response. At 2:53 p.m. of the same day he was given a second 10 mg. intravenously. At 2:56 p.m. he caught a baseball when it was thrown to him and soon was playing catch with the nurse. At 3 p.m. he got in line for supper, after going to the toilet without being told to do so. In this short time he demonstrated more voluntary movement and more mental alertness than had been seen during the total of his 21 years in the hospital. This new pattern lasted approximately five hours. On Sept. 9, 1956, the experiment was repeated, with the administration of a single 30-mg. intravenous injection. The response was even more dramatic. In less than five minutes the patient was not only playing catch but was able to examine the ward as if it were his first time to see parts of it, although he had been a patient there for 21 years.

Case 2.—A 41-year-old male had been admitted to the hospital in 1939. During the 17 years that he had been a patient he had never been known to move without help. If his arms or legs were placed in some unorthodox position, they would remain as placed for hours. He needed help and prodding for his every act. At 2:55 p.m. on Sept. 5, 1956, he was given 10 mg. of methylphenidate parenteral solution intravenously. At 2:58 p.m. he was given the second 10 mg. intravenously, and at 3 p.m. he was given another 10 mg. intravenously, thus making a total of 30 mg. At 3:05 p.m. he was playing catch with the nurse and the patient discussed above. His mental awakening lasted approximately four and one-half hours. On Sept. 9, 1956, the experiment was repeated, with the administration of a single intravenous injection of 30 mg. Within five minutes he was playing catch, although he seemed more interested in his hands —as if testing every possible movement.

Comment

On Sept. 12, 1956, the 11 chronically regressed, underactive patients of the special group who had been tested with methylphenidate parenteral solution were tested with placebo injectable solution. Four received as much as 100 mg. (10 cc.) intravenously, without any change from their old pattern. The day after the placebo had been given, the 11 patients were then given 20 to 30 mg. of methylphenidate parenteral solution intravenously. All responded to the drug as they had previously. During the experiments, blood pressure level and pulse and respiration rates were recorded. No changes of significance were recorded.

Therapy with methylphenidate parenteral solution was not continued in 4 of the 11 patients, in order that we may clinically evaluate the activity of other analeptics. This work is in a preliminary stage. However, at this time, none of the other drugs so far tested have produced the dramatic response seen with methylphenidate parenteral solution. Six of the seven patients in whom therapy with orally given methylphenidate has been continued have shown a slow, steady improvement, almost in proportion to the time and retraining they have been given. The improved condition of one patient is maintained only when he is given methylphenidate parenteral solution intravenously or intramuscularly.

Because of its safe, fast action in overcoming most of the so-called side-reactions of the tranquilizing drugs and because of the improvement we have witnessed in chronically underactive patients, the parenteral form of methylphenidate gives promise of opening new doors in our quest to eradicate mental illness. Further studies are recommended.

The methylphenidate hydrochloride used in this study was supplied as Ritalin parenteral solution (1%) by Ciba Pharmaceutical Products, Inc., Summit, N.J.

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GENERALIZED CYTOMEGALIC INCLUSION DISEASE IN NEWBORN INFANTS

McLemore Birdsong, M.D., David E. Smith, M.D., Fred N. Mitchell, M.D.
and
J. Hicks Corey Jr., M.D., Charlottesville, Va.

• *Generalized cytomegalic inclusion disease is an intrauterine infection that, in its most serious form, causes symptoms at or soon after birth. The two infants here described had icterus, extensive petechial or ecchymotic hemorrhages, hepatomegaly, splenomegaly, and various laboratory findings indicating a severe blood dyscrasia. One infant died an hour after birth; the other at birth exhibited signs of hemolytic icterus and an anemia that progressed at first but was ultimately controlled. Numerous fresh urine specimens obtained from the second infant during the first two weeks yielded a sediment that, on fixing and staining, exhibited enlarged cells with typical cytoplasmic as well as intranuclear inclusions. The second infant is one of three now known to have survived this disease. The causative organism is a salivary gland virus that probably infects a large proportion of the population subclinically at an early age. The infant who survived was treated with vitamin K intramuscularly, benzathine penicillin G orally, prednisolone, and corticotropin.*

The purpose of this paper is to discuss the clinical picture, etiology, and pathology of cytomegalic inclusion disease as seen in infancy and to describe two cases. One case was diagnosed by the examination of urinary sediment and is the third reported case with recovery of the patient; the second case was diagnosed at autopsy and is typical of the usual past experience with this disease.

Report of Cases

CASE 1.—A 2,280 gm. (5 lb.) female was born after eight months gestation terminated by a normal labor and an uncomplicated spontaneous delivery. Both parents were blood type O, Rh positive. At birth the infant was moribund and had severe jaundice, with ecchymoses noted over the back. The head and buttocks appeared abnormally small. A grade 1 precordial murmur was heard, and the cardiac rate was found to be variable. The respirations were irregular, numbering only one to two per minute. The liver was palpable at the iliac crest, and the spleen was similarly enlarged. Ecchymoses became progressively widespread, and the patient's condition deteriorated rapidly, with death occurring one hour after birth. A venipuncture was performed shortly after birth, and bleeding continued for several minutes after death.

The white blood cell count was 80,000 per cubic millimeter, corrected to 38,100; a differential count showed 4 band cells, 18 polymorphonuclear cells, and 78 lymphocytes. The hemoglobin level was 10 gm. per 100 cc. There were 300 nucleated red blood cells per 100 white blood cells, there was marked anisocytosis of the red blood cells, and there were no demonstrable platelets. The infant's blood type was O, Rh positive. The direct Coombs' test was negative, and the Wassermann test was negative. Studies on the mother's blood failed to reveal any abnormal agglutinins. It was impossible to carry out other studies.

Postmortem Examination.—On gross examination the principal findings were slight icterus, widespread petechiae, and marked enlargement of the spleen and liver. Petechiae were present on all the body surfaces; in the mucosa of the esophagus, stomach, ileum, colon, and urinary bladder; in the pleura; and in the kidneys. The heart was normal. The lungs were airless, moist, and heavy. They contained hemorrhages that were particularly prominent in the interlobular septums. The abdomen contained a small amount of icteric fluid, and there was a generalized enlargement and reddish discoloration of the lymph nodes in the mesentery, mediastinum, and retroperitoneal regions. The liver was greatly enlarged to a weight of 156 gm. and extended 5 cm. below the costal margin, as did the spleen, which weighed 52 gm. The kidneys were slightly enlarged, and their cortical architecture was obscured by multiple dark hemorrhagic areas. In the cranial cavity there was a small amount of clotted blood of undetermined origin on top of the tentorium. The brain was of normal size and configuration and contained no lesions on sectioning.

Microscopically the principal lesions were the cells with inclusions and widespread extramedullary hematopoiesis, consisting principally of erythroblastic cells but including myeloblasts and usually accompanied by appreciable interstitial hemorrhage. The inclusions (fig. 1) were of typical type and occurred in greatly enlarged cells. The intranuclear inclusions were very large, ovoid, amphophilic, and rather homogeneous. They were surrounded by halos devoid of chromatin, and the chromatin was condensed upon the distended nuclear membrane. Examples of the irregular basophilic cytoplasmic inclusions were much less numerous than those of the intranuclear inclusions. These inclusions were present in the ducts of the parotid gland; large cells that lay loose in the alveoli of the lungs; the ducts; and other epithelial cells in the portal spaces of the liver, the pancreas (where the islets of Langerhans were particularly involved), tubular epithelium in the kidney, and the pituitary, thymus, and thyroid. One example was found in an endothelial cell in a cervical node. In the brain, several inclusion-bearing cells were present in the neonatal glial mass beneath the ependyma of the lateral ventricles.

Extramedullary hematopoiesis accompanied by significant hemorrhage (fig. 2) was present in the kidneys, liver, and lungs. Hematopoietic tissue without hemorrhage was seen in the spleen, lymph nodes, and thymus and to a slight extent in the epicardium, adrenals, uterus, and pituitary. The liver showed considerable disarrangement in addition to the inclusion cells and the hematopoiesis and hemorrhage. The liver cell cords were poorly developed, and the portal spaces were enlarged and contained irregular and broken cholangioles and an infiltration by lymphocytes and leukocytes. The bone marrow was solidly cellular and contained an excessive proportion of erythroblastic cells but no other abnormalities.

CASE 2.—A 2,580 gm. (5 lb. 11 oz.) male was admitted by birth to the newborn service of the University of Virginia Hospital on Oct. 28, 1955. The mother, blood type A, Rh positive, was a primigravida who had experienced an uncomplicated nine-month pregnancy. Labor was complicated by mild preeclampsia. Delivery was facilitated by the use of low forceps. The infant demonstrated the following positive physical findings: (1) a mild degree of icterus of the scleras, a generalized petechial and purpuric eruption, and scaling of the hands; (2) lethargy, although the Moro reflex was active and bilaterally equal; and (3) the spleen palpable 4.5 cm. below the left costal margin and the liver palpable 2 cm. below the right costal margin. On the second day of life a grade 1, high-pitched, systolic, nonradiating murmur was heard at the left sternal border in the fourth and fifth left intercostal spaces.

The initial laboratory studies demonstrated anemia, bilirubinemia, prolonged bleeding time, and poor clot retraction. The bone marrow showed no megakaryocytes, an increased number of nucleated red blood cells, and an over-all decrease in cellular-

From the departments of pediatrics and pathology, University of Virginia School of Medicine.

Fig. 1.—Intranuclear and cytoplasmic inclusion bodies of the salivary gland virus type in an enlarged renal tubular epithelial cell (case 1). (× 1,000).

ity. Subsequent blood studies showed progressive anemia, which eventually stabilized, reticulocytosis, and a marked depression of the thrombocytes. Results of other laboratory tests included the following data: Blood type O, Rh negative; Coombs' test negative; Kline test negative; blood cultures negative; and parental blood group incompatibilities absent. Maternal platelet count was 110,000 per cubic millimeter (direct), and studies for toxoplasmosis on the infant and mother were negative. Results of Van den Bergh's test were direct negative and indirect 6 mg. per 100 cc. on Oct. 28, 1955, the indirect being 0.2 mg. per 100 cc. on Nov. 28, 1955. Repeated white blood cell counts and smears were regarded as normal. A urine specimen on Nov. 1, 1955, contained 2 + albumin and 3 to 5 coarse granular casts but was otherwise normal. Stool examination, including trypsin activity, was normal. At birth the coagulation time was 3 minutes, 24 seconds; clot retraction time two hours; and the bleeding time 30 minutes. Thymol turbidity was 4.6 units, and the methylene blue dye test was negative. The platelet counts and serum protein analysis are given in the table. X-rays of the skull and long bones were normal, and funduscopic examination by an ophthalmologist failed to show any abnormalities. Beau's lines were noted on the 16th hospital day.

Fig. 2.—Extramedullary hematopoiesis in interstitial tissue of kidney (case 1). These foci were often accompanied by hemorrhage (× 240).

Upon admission to the nursery for newborn infants, the patient was given 5 mg. of vitamin K intramuscularly. Oral administration of benzathine penicillin G (Bicillin), 50,000 units, was begun twice daily. The infant was placed on therapy with prednisolone (Meticorten) given in divided doses of 30 mg. the first day, 20 mg. the second day, and 15 mg. daily thereafter for a period of two months, at which time the steroid therapy was discontinued while corticotropin was administered. During the first two weeks of the 28-day hospitalization, numerous fresh urine specimens were obtained. The sediment was fixed in formaldehyde, and the smears were stained with hematoxylin-eosin and Wright-Giemsa stains. Cells typical of cytomegalic inclusion disease were demonstrated on several occasions (fig. 3). During the three and one-half months of follow-up examinations, clinical progress was satisfactory, without evidence of jaundice and purpura, even though there was some persistence of anemia and diminished production of megakaryocytes on bone marrow examination.

Fig. 3.—Two epithelial cells with intranuclear inclusions from urinary sediment (case 2). The cells were generally sufficiently disrupted that no clear examples of the cytoplasmic inclusions were found (× 1,300).

Comment

History, Etiology, and Clinical Findings.—The salivary gland viruses are the etiological agents of human cytomegalic inclusion disease and of related conditions in many species of animals. These viruses are ubiquitous infectious agents whose names are derived from the early recognition that their characteristic lesions occurred most frequently in salivary glands. The inclusions formed by the action of the viruses were first confused with protozoa, but in 1926 Cole and Kuttner [1] showed that typical lesions in guinea pigs

were due to a transmissible and filterable agent. It was then discovered that there were a number of agents that produced the characteristic lesions in various animals but that each strain was species-specific. Except on inoculation into very young animals, the infections produced by these viruses are innocuous.

Knowledge of the human infection has rested on the analogy of the morphological changes in human tissues with those in animal tissues until recently, when Smith [3] successfully propagated the human virus in tissue cultures. Evidence of infection by this virus may be found in tissues under three principal circumstances: (1) incidentally in the salivary glands, (2) in various organs of children and adults who have been ill with other diseases, and (3) disseminated throughout many organs in the newborn infant.

The incidence of the typical inclusions within the salivary glands in routine autopsies of children has been reported as 10 to 32%.[3] This strongly suggests that this virus subclinically infects a large proportion of the population at a relatively young age. The disseminated occurrence of the inclusions in older children and adults has usually been observed in association with other severe diseases and is probably beyond the salivary gland. The generalized disease in the newborn infant appears to be a primary infection by the virus.

Although no significant illness has ever been recognized in the mothers of these infants, it is very interesting that the mothers are often primigravida and from relatively isolated rural homes or communities. Such circumstances suggest that this condition results when the mother has an initial, subclinical infection with the virus coincidental with her pregnancy. As no cases have been reported of the occurrence of generalized infantile cytomegalic inclusion disease in more than one child of a given mother and since it appears that most adults have had the infection at some time in their lives, it appears that infection of the mother prior to her pregnancy presents no danger.

The generalized infantile disease may be due to either an intrauterine or a postnatal infection. In the case reported by Gallagher,[4] an infant developed a pulmonary infiltration that progressed to cyst formation in early infancy. On removal of the involved lobe of the lung when the child was 2 months old, typical inclusion bodies were discovered in the bronchial epithelium. This infant survived and apparently has had no recurrence of the disease. Several other cases, such as that of Bacala and Burke,[5] present histories of normal neonatal periods with the subsequent onset of illness during early infancy. Varied symptoms, including vomiting, diarrhea, failure to gain weight, chronic eczema, convulsions, and cyanosis, were described by these authors and they suggested that signs and symptoms might be expected to vary depending upon the organs and tissues most severely damaged by the virus. Cases of congenital brain damage, with calcification, similar to those caused by toxoplasmosis have also been described, and it is suspected that some of these infants may survive.[6]

In the most serious form of the disease, symptoms occur at or soon after birth. This severe generalized infantile disease, as illustrated by the two cases in this report, is apparently due to an intrauterine infection. The signs and symptoms are immediately apparent in the postnatal period, and evidence of the active disease has been seen in stillborn infants. As in hemolytic disease of fetus and newborn infant, the infants are born with some evidence of the disease and develop alarming symptoms in the first few days. The usual signs and symptoms are jaundice, hepatomegaly, splenomegaly, purpura, thrombocytopenia, and hemolytic anemia. Other less frequently described findings are intracranial calcifications, cerebral hemorrhage, convulsions, and cyanosis.[6] Late-occurring symptoms include vomiting, diarrhea, failure to gain weight, and chronic eczema.[5]

Platelet Counts and Serum Protein Analysis of Patient (Case 2) Who Recovered from Cytomegalic Inclusion Disease

	Platelet Count Cu. Mm.
10/28/55	300,000
10/29/55	4,000
11/ 1/55	20,000
11/ 8/55	12,000
11/10/55	16,200
11/14/55	12,700
11/28/55	58,000
12/15/55	68,000
1/ 6/56	79,000
2/ 9/56	114,000
3/ 2/56	63,000
3/ 6/56	58,000

Serum Protein Analysis 2/14/56	Values Found	Normal Values
Total Protein Gm./100 Ml.	6.67	7.35
Serum Protein Pattern (Paper Electrophoresis)		
Albumin, %	52.7	59.4
Alpha 1, %	6.3	6.0
Alpha 2, %	14.4	9.5
Beta, %	15.6	10.7
Gamma, %	11.0	14.4

The differential diagnosis is that of jaundice, hemolytic anemia, and thrombocytopenia. Diseases that should be considered are hemolytic disease of fetus and newborn infant (Rh, ABO, and other blood incompatibilities), congenital syphilis, spherocytosis, nonspherocytic hemolytic anemia, congenital obstructions of the bile ducts, acute sepsis, toxoplasmosis, and galactosemia, as well as other less common considerations. Fetterman [7] was the first to show that the diagnosis can be made by careful examination of fresh urinary sediment. The finding of tubular epithelial cells with the characteristic inclusions in the sediment is diagnostic of cytomegalic inclusion disease. At the present time, this is the only way to make the diagnosis in the living patient, except by removal of tissue for histological study.

Treatment

At this writing little is known concerning the treatment of cytomegalic inclusion disease. Margileth,[8] in the medical management of the first surviving patient,

used cortisone. In our surviving patient steroids were also used. The rationale for steroid therapy was based on recognition of the severe hemolytic features and the knowledge that in other hemolytic diseases cortisone has been helpful. The mechanism of the hemolytic process is not known exactly, but it seems reasonable to assume that, since cytomegalic inclusion disease is caused by a virus, abnormal antibodies might account for the finding of a hemolytic process in these cases. Cortisone has also been used successfully in the treatment of thrombocytopenia, which is a characteristic feature of this disease and which was extremely severe in our patient.

Exchange transfusion has been advocated but not yet reported in the treatment of cytomegalic inclusion disease. The hematological findings represent those of a hemolytic anemia secondary to the viral infection. It would seem that exchange transfusion would be useful in temporarily decreasing the circulating antibody, assuming that an abnormal antibody is present. This form of therapy should be given serious consideration in cases diagnosed in the future. Gamma globulin has been recommended in the treatment of this disease, but we can find no rationale for its use. Antibiotics may be used prophylactically, with no idea of affecting the course of the primary disease process.

Summary

Of two cases of generalized neonatal cytomegalic inclusion disease, in one, a nonfatal case, the diagnosis was made clinically and confirmed by demonstration of inclusions in cells in the urinary sediment; in the other, the clinical and pathological features were typical of most previously reported cases. This disease is an intrauterine virus infection and is characterized by icterus, hemolytic anemia, thrombocytopenia, and other manifestations. At present there appears to be a rationale and clinical evidence for the use of cortisone in treatment of recognized cases. Exchange transfusions might be useful, but specific therapeutic agents are not presently available.

Addendum

The patient in case 1 was seen on Sept. 14, 1956, at which time his physical examination was negative and his weight was 8,504.9 gm. (18 lb. 12 oz.). Both his physical and mental development appeared to be normal.

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CLINICAL NOTES

FATAL AGRANULOCYTOSIS OCCURRING DURING PROMAZINE (SPARINE) THERAPY

Doris J. Woodward, M.D.
and
James D. Solomon, M.D., Ph.D., Washington, D. C.

Promazine (Sparine) is 10-(3-dimethylaminopropyl) phenothiazine hydrochloride, one of the newer ataraxic drugs recently introduced into clinical practice. It is chemically related to chlorpromazine, both compounds containing the phenothiazine nucleus. The structure of promazine is the structure of chlorpromazine minus the chlorine atom. Promazine has been used in the management of patients with acute mental disturbances [1] and at this stage is not recommended for patients with chronic conditions. Nevertheless, a clinical trial in such patients was planned. In March, 1956, it was decided to give a course of promazine therapy to 97 patients (50 female, 47 male), all with chronic conditions, who had been hospitalized for from 5 to 25 years. So far as is known, there has been no report in the literature of a case of agranulocytosis resulting from promazine therapy. In order to furnish the first known direct evidence of toxic effects of promazine on the bone marrow, we consider it of interest to report a case of fatal agranulocytosis occurring in a patient during administration of this drug.

From the Psychiatric and Medical Service, St. Elizabeths Hospital.

Report of a Case

A 57-year-old female was admitted to the psychiatric service on Feb. 25, 1937, with a diagnosis of schizophrenic reaction, paranoid type. The onset of her mental illness was insidious and extended over a period of years. On admission, the physical examination showed nothing essentially abnormal. Psychiatric observation revealed no significant changes over the years. She was seclusive, irritable, hostile, and noisy and did not take part in ward activities. Her speech was rambling, incoherent, and at times difficult to understand because of a marked German accent. She had hallucinosis. The patient had not previously received any of the ataraxic drugs, and there was no history of any convulsive disorders. Blood studies prior to promazine therapy showed a white blood cell count of 8,200 per cubic millimeter, a hemoglobin level of 15.4 gm. per 100 cc., and a hematocrit value of 42%. The total serum bilirubin level was 0.32 mg. per 100 cc.,

with direct 0.1 mg. and indirect 0.22 mg. Urinalysis (not a catheterized specimen) showed a specific gravity of 1.022 and was negative for acetone, albumin, and sugar, with an occasional white blood cell being seen on the microscopic examination. X-ray of the chest was negative.

Promazine therapy was started June 4, 1956. The initial dosage was 100 mg., 200 mg., and 400 mg. for the first, second, and third days respectively. After the third day, the dosage was increased by 100 mg. per day each week until a total daily dosage of 1 gm. was reached (July 16, 1956). All medicaments were given by mouth and in divided doses three times daily. On July 3, 1956, the three times daily dosage was changed to four times daily. Temperature, pulse and respiration rate, and blood pressure were taken daily during the first two weeks of therapy and showed no marked variation from normal. The patient's mental status showed little, if any, improvement at this period of treatment.

On July 6, the 31st day of promazine therapy, blood studies revealed a white blood cell count of 3,800 per cubic millimeter, with a differential count of 60% neutrophils and 40% lymphocytes. The hematocrit value was 38%. The patient's temperature was normal, and physical examination revealed no evidence of infection, sore throat, or ulceration of the mouth. No enlarged lymph nodes were palpable. The treatment with promazine was continued, with daily inspections and observations of the patient.

On July 20, the patient was noted to be unusually confused and unsteady on her feet and was reported to have fallen in the bathroom late in the afternoon. Her temperature was normal, and physical examination revealed no positive findings. On July 21, the 46th day of therapy, the patient had a petit mal seizure lasting two minutes. There was no injury. At this time there was a rectal temperature of 102.8 F (39.3 C). The patient was responsive and there were no positive physical findings. She was given 10 grains (0.6 gm.) of aspirin and fluids by mouth.

On July 22, the patient's temperature in the morning was up to 103 F (39.4 C). The only positive physical finding was fecal impaction. An enema was given. The fluid intake for the previous 24 hours had been 1,590 ml., and the output was 400 ml. Promazine was withdrawn. At this time, medical consultation was requested, and the patient was transferred to the medical and surgical branch in the afternoon. Physical examination at the medical and surgical branch revealed these positive findings: scleras, slightly icteric; lungs, dulness at left base with increased breath sounds and a few coarse rales; heart, pulmonic second sound greater than the aortic second sound, with a loud grade 2 systolic murmur in all areas; and abdomen, protuberant, slightly tense, no palpable organs, and fecal impaction. The neurological examination revealed active tendon reflexes bilaterally. There was extreme weakness in both legs, with hypotonia. The patient did not appear acutely ill.

A roentgenogram of the chest was essentially normal, and urinalysis showed a specific gravity of 1.004, traces of albumin, an occasional hyalin cast, white blood cells, and many bacteria. A blood culture was taken and was reported sterile. A blood cell count showed 575 white blood cells per cubic millimeter, with 90% lymphocytes. The hematocrit value was 33% and the hemoglobin level 9.3 gm. per 100 cc. A throat smear and culture showed beta-hemolytic streptococci, gamma streptococci, nonhemolytic micrococci, and Escherichia coli.

On July 23, the white blood cell count was 600 per cubic millimeter, with no mature neutrophils, and a sternal puncture was done for a bone marrow study. The bone marrow showed complete maturation arrest of the granulocytic series, with only myeloblasts seen. There was an increase in the mononuclear series, such as lymphocytes, plasma cells, and reticular cells. Urinalysis showed a specific gravity of 1.007 and was positive for hemoglobin. Microscopic examination revealed increased cylindruria. The patient showed increased inability to move her legs. There were small areas of ecchymosis in both eyes. A diagnosis of agranulocytosis due to drug reaction was made.

Medical treatment consisted of the intramuscular administration of tetracycline (Achromycin), 200 mg. every four hours; procaine penicillin, 600,000 U.S.P. units once daily; procaine penicillin for aqueous injection, 500,000 U.S.P. units every two hours; and cortisone, initially 200 mg. administered intramuscularly, then 100 mg. every eight hours. The patient was given 40 units of corticotropin (ACTH) with the first dose of cortisone. Because of the decrease in red blood cells, 500 ml. of blood was administered July 23. One concentrated, salt-poor unit of liquid normal human serum albumin (25 gm. albumin in 100 ml.) was also given. The patient's intake and output of fluid was measured, and supportive fluid was administered intravenously.

On July 24, cortisone, 100 mg. three times daily, was given, and on July 25 the cortisone was decreased to 40 mg. every six hours. At this time, clinical jaundice was evident and agranulocytosis of the oral cavity and oropharynx was noted. The abdomen showed moderate distention on the morning of July 26. That afternoon acute pulmonary edema with auricular fibrillation developed, and the blood pressure fell to 60/40 mm. Hg. The patient for the first time appeared critically ill. She was digitalized with lanatoside C (Cedilanid). Oxygen nasally and methoxamine (Vasoxyl) hydrochloride, 1 ml. intravenously and intramuscularly, were administered. There was complete renal shutdown, and the blood pressure failed to rise above 60/40 mm. Hg. In the early morning of July 27, the patient died.

Results of additional laboratory studies during her course in the hospital were as follows. On July 24, total bilirubin level was 5.54 mg. per 100 cc., with direct 3.99 mg. and indirect 1.55 mg., thymol turbidity, 4 units (Shank-Hoagland); cephalin flocculation, negative in 24 hours; serum alkaline phosphatase, 5 Bodansky units; and prothrombin time, 16.9 seconds (control) and 14 seconds. The white blood cell count was 350 per cubic millimeter in the morning and 125 in the afternoon, with 90% lymphocytes in both counts. The hematocrit value was 32% and the hemoglobin level 10 gm. per 100 cc. Urinalysis showed numerous granular casts, 1+ albumin, and 2+ sugar. On July 25, the total bilirubin value was 10.6 mg. per 100 cc., with direct 8.4 mg. and indirect 2.2 mg. The white blood cell count was 450 per cubic millimeter, with 50% lymphocytes; hemoglobin level 8.9 gm. per 100 cc.; and hematocrit value 29%. The nonprotein nitrogen level was 47 mg. per 100 cc. on the morning of July 26. The gross findings at autopsy were pulmonary edema and atelectasis, acute ulcerative colitis, fatty metamorphosis of the liver, and agranulocytosis.

Comment

Apparently most of the ataraxic drugs are capable of depressing the bone marrow when used in sufficient dosages and over long periods of time. The advisability of frequent blood cell counts during the administration of these ataraxic drugs cannot be overemphasized.

Summary

A fatal case of agranulocytosis occurred in a patient on the 48th day of administration of promazine (Sparine). The dosage had been instituted at 100 mg. per day and reached a maximum of 1 gm. per day in four divided doses over a 42-day period.

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Improvements in Cancer Survival Rates.—The Connecticut Cancer Record Register has information on 75,494 cancer cases diagnosed from 1935 through 1951. Follow-up information reveals that the outlook for survival is improving for some forms of cancer. Marked increases in five-year survival rates were observed for patients with cancers of the large intestine, rectum, cervix, corpus, prostate and endocrine glands. Both earlier case finding and more effective utilization of available therapeutic technics apparently were factors in increasing the proportion of cancer patients alive five years after diagnosis. Effective use of technics has had a more measurable effect in recent years. Further increase in survival must be predicated on research for better diagnostic and therapeutic methods.—M. H. Griswold, M.D., S. J. Cutler, M.A., and H. Eisenberg, M.D., *The New England Journal of Medicine*, June 7, 1956.

COUNCIL ON FOODS AND NUTRITION

Report to the Council

The following paper was presented at the symposium, "Some Inorganic Elements in Human Nutrition," in Nashville, Tenn., April 4, 1955. This symposium was sponsored jointly by the Nashville Academy of Medicine, the Vanderbilt University School of Medicine, and the Council on Foods and Nutrition. This report is the final of the series, others of which appeared in THE JOURNAL *April 21, June 9, Sept. 15, and Nov. 10, 1956.*

PHILIP L. WHITE, Sc.D., *Secretary.*

PHYSIOLOGICAL BASIS OF POTASSIUM THERAPY

Daniel C. Darrow, M.D., Kansas City, Mo.

Rational treatment of disturbances of the body potassium level is based on the physiology of water and electrolytes. Beginning with Ringer's studies of the effects of electrolytes on the heart, numerous investigations have indicated that the activity of all cells is altered by changes in the concentration of the potassium surrounding the cells. High plasma concentrations exert their most important effect on the heart, because arrhythmia and heart block are produced at plasma potassium concentrations of 8 to 10 mEq. per liter.[1] A flaccid paralysis of skeletal muscle has been observed at high concentrations in some patients with advanced renal failure. The paralysis resembles that seen with low plasma potassium levels except that the electrocardiograms are characteristic of those of patients with potassium intoxication. The high-peaked T waves are the earliest electrocardiographic alterations, but absent P waves, spreading QRS complexes, and more advanced disturbances develop later.

When the potassium concentration in plasma is low, a patient's first complaint is usually lassitude and weakness. The electrocardiograms often show flat T waves that may be inverted. Little evidence of cardiac failure is present in mild deficiency, but when potassium deficiency is severe and prolonged, circulatory failure and myocardial necrosis occur. The skeletal muscles show diminished tone, weakness, and, under certain circumstances, flaccid paralysis identical with that described in familial periodic paralysis. The weakness is usually more pronounced in the lower extremities, but the muscles of respiration may be sufficiently involved to interfere with their functions. The smooth muscles also show decrease in tone, producing intestinal and gastric distention, nausea, occasionally vomiting, and finally paralytic ileus. Indeed, potassium deficiency must always be considered a possible cause of paralytic ileus, although other disturbances produce the same picture. The paralysis in both smooth and skeletal muscles is apparently caused by a failure of myoneural conduction that is readily reversed by an increase in serum potassium concentration. Potassium also alters other neural reactions. Certain patients with low serum calcium levels do not have tetany when the serum potassium level is low, but tetany is manifest when potassium concentration rises to normal.[2]

In a study made in 1945, the implications of the changes in muscle composition observed in rats were discussed.[3] On the basis of these experiments it was possible to deduce many of the clinical states of potassium deficiency in patients, which subsequent studies have demonstrated. The quantitatively important alterations in potassium in the body are accounted for by changes in potassium in muscle. There is no evidence of increased storage of potassium in cells except for the slight rise that accompanies an increase in serum concentration. This increase in cell potassium levels does not persist when normal plasma concentrations are restored. A decrease in the muscle potassium level may be great, but it is not necessarily accompanied by decreases in serum concentrations. As a result of diets low in potassium, muscle potassium levels may decrease to half the normal value.[4] Usually about two-thirds of the decrease is replaced by an increase in intracellular sodium. This is equivalent to a loss of about 25 mEq. of potassium per kilogram and an increase of intracellular sodium of about 17 mEq. per kilogram of body weight. Clinical studies indicate that essentially the same changes occur in patients. Evaluation of the clinical states is closely related to the experimental studies.

The potassium content of the cell is primarily dependent on the cell's structural and metabolic integrity. It is not known by what mechanism the cells maintain a high concentration of potassium and a low concentration of sodium while surrounded by extracellular fluids with a low potassium and a high sodium concentration. Water is exchanged rapidly between extracellular and intracellular fluids, but the rate of net exchange of sodium and potassium is somewhat limited. It is clear that potassium leaves and sodium enters the cells when cellular metabolism ceases. A more limited exchange of this type probably occurs when metabolic processes are impaired. Anoxia and insulin deficiency are examples of this type of altered exchange that can be reversed.

The therapeutic administration of potassium first requires treatment that restores normal cellular metabolism as far as this is possible. In shock and dehydration, replacing deficits of water and extracellular

From Children's Mercy Hospital and the Department of Pediatrics, University of Kansas.

electrolytes is the first step in treating potassium deficiency. Although restoration of extracellular water and electrolytes is the most important means of correcting the circulatory failure of dehydration and deficit of sodium and chloride, transfusions make this therapy definitely more effective in experimental animals and patients. In hemorrhagic and oligemic shock, transfusions are essential. Likewise, insulin is necessary in diabetic coma in order to facilitate the uptake of potassium by cells depleted of this ion. Administration of water, sodium, and chloride is equally important in patients who have suffered large losses; administration of oxygen is indicated in some anoxic patients. These measures that restore cellular metabolism should be carried out before the administration of potassium is started.

Rapid restoration of cellular metabolism in a patient with large cellular deficits of potassium may lead to rapid transfer of extracellular potassium to the cells. Consequently, symptoms of low concentration of potassium in serum are likely to develop rapidly. If renal function is good, the administration of potassium may be started early, but it should be started slowly and in anticipation of the decrease in serum potassium concentration. Owing to the particularly rapid restoration of cell metabolism in diabetic coma, frank symptoms of potassium deficiency are especially likely to develop in patients treated without potassium at the time when the effects of insulin appear. Patients in alkalotic states with potassium deficiency are also likely to develop symptoms of hypokalemia because alkalosis increases the tendency to transfer potassium from extracellular to intracellular fluids. In diabetic coma, skeletal muscle weakness and paralysis have been observed, whereas in alkalosis, intestinal distention, vomiting, and paralytic ileus are more frequent. In other types of acidosis with potassium deficiency, a decrease in serum potassium concentration during treatment is likely to develop more slowly. The reason for this is that, initially, the serum potassium concentration is likely to be somewhat high, and transfer of potassium from extracellular to intracellular fluids is retarded by acidosis. If sodium bicarbonate or its equivalent is given to increase rapidly the plasma bicarbonate level, a decrease in serum potassium concentration is likely to be accelerated.

These statements are based on clinical observations and experimental studies. When muscle is placed in Ringer's solution with a given potassium concentration, a high pH of this solution leads to transfer of potassium to the cells while a low pH produces the opposite effect. This observation has been confirmed in nephrectomized dogs receiving injections of ammonium chloride or sodium bicarbonate. In otherwise normal dogs, production of metabolic acidosis and alkalosis demonstrates an inverse relationship between serum pH and serum potassium concentration that is not explained by a change in total body potassium.[8] In dogs previously depleted of potassium, the same inverse relationship is manifest; however, the serum potassium concentrations remain somewhat lower. As would be anticipated, potassium tends to enter the cells as serum potassium concentration rises, and vice versa. This reaction is more or less independent of the shifts accompanying changes in pH.

The clinical implications of these observations are reasonably clear. Serum potassium concentration reflects the changes in serum pH and the concentration of potassium in cells. The serum potassium concentration is likely to be low in alkalosis even if the cell potassium level is relatively normal but especially low when cellular potassium deficiency is present. In alkalosis, serum potassium concentration is not likely to be high unless renal function is impaired and the cell potassium level is relatively normal or unless disturbances in cellular metabolism have developed. In acidosis, serum potassium concentration is likely to be normal or high despite cellular deficits. Low serum potassium concentrations in acidosis usually indicate considerable deficits of intracellular potassium. Disturbances in cellular metabolism and renal function must also be considered in evaluating potassium concentration in acidosis.

Renal response to respiratory changes in acid-base equilibrium tends to exaggerate the changes in plasma concentration produced by the alteration in carbon dioxide tension. In respiratory acidosis, carbonic acid donates hydrogen ions to buffers, thereby forming undissociated weak acids and raising serum bicarbonate. The kidneys further increase bicarbonate concentration by excreting hydrogen ions. The process is, in effect, an exchange of plasma chloride for bicarbonate of the glomerular filtrate. In this process, the muscle potassium level is well maintained.[9] In respiratory alkalosis, the exchange for sodium of hydrogen ions freed from undissociated weak acids decreases plasma bicarbonate. The kidneys exaggerate the decrease in bicarbonate by retaining hydrogen ions. This is accomplished by exchanging plasma bicarbonate for chloride of the glomerular filtrate. It is not known whether serious deficits of potassium develop in respiratory alkalosis. In any case, replacement therapy is seldom indicated, since the kidneys readily restore normal body electrolyte balance when carbon dioxide pressure becomes normal.

In metabolic acidosis, the normal kidneys tend to restore normal extracellular concentrations if sufficient sodium, potassium, chloride, and water are available. The fundamental operation that restores a low serum bicarbonate value is the excretion of hydrogen ions. Experimental acidosis caused by administration of hydrochloric acid to dogs is corrected first by excretion of the excess of chloride with sodium and then potassium. The excess of chloride is reduced, but deficits of sodium and potassium are likely to develop; hydrogen ions are not excreted, and bicarbonate concentration is not restored. Only after 1 or 2 days are sufficient ammonium ions formed to conserve sodium and potassium and to excrete hydrogen ions effectively. These observations indicate that in metabolic acidosis abundant sodium and potassium are required for renal compensation. The experiments also show

that deficits of potassium as well as of sodium are likely to develop. The changes in body composition are not confined to extracellular fluids.

In metabolic alkalosis, the normal kidneys also tend to restore normal plasma concentrations if sufficient sodium, potassium, chloride, and water are available. The fundamental operation is retention of hydrogen ions. This is accomplished, in effect, by excretion of bicarbonate or organic acids with sodium and potassium. Metabolic alkalosis is usually accompanied by a relative or absolute excess of sodium in the body. Accordingly, the renal compensation is only likely to produce deficits of potassium. The course of events is well illustrated by experiments on rats given large loads of sodium bicarbonate and variable amounts of potassium chloride.[7] Alkalosis, which developed only when the intake of potassium was low, was always accompanied by a decrease in muscle potassium and an increase in intracellular sodium. Apparently excretion of a certain amount of potassium is necessary to preserve plasma chloride concentrations and to prevent alkalosis. These observations fit in well with clinical experience, which shows that metabolic alkalosis is not corrected despite an abundant excretion of sodium and chloride when potassium deficiency develops.[8]

The plasma bicarbonate concentration varies directly with intracellular sodium and inversely with the muscle potassium level in experimental rats. Clinical observations fit in well with these observations if due attention is paid to the experimental conditions. Metabolic acidosis was produced by removal of sodium bicarbonate by peritoneal exchange and maintenance of rats on a diet containing abundant potassium and chloride but no sodium. Metabolic alkalosis was produced by peritoneal exchange of body chloride for bicarbonate. The rats received a diet abundant in sodium and potassium but no chloride. Potassium deficiency was produced by injections of desoxycorticosterone acetate in rats on a low-potassium diet with an abundance of sodium chloride. Sufficient time was allowed in all experiments to permit renal adjustment to the experimental conditions. Deficit of chloride and potassium resulted in essentially the same changes in the muscle and serum, that is, metabolic alkalosis, high serum bicarbonate values, and low chloride concentrations with low muscle potassium and high intracellular sodium levels. Deficit of sodium bicarbonate resulted in metabolic acidosis and low intracellular sodium and high muscle potassium concentrations. Changes in the metabolic alkalosis and potassium deficiency are frequently met in clinical medicine; however, metabolic acidosis is not often seen in patients when an abundance of potassium is available.

Protein milk produces metabolic acidosis accompanied by retentions of potassium and chloride.[9] Muscle potassium concentration is probably high in such cases. Acidifying salts may have a similar effect if the intake of potassium is high. Usually the losses of electrolyte, which produce metabolic acidosis, result in deficits of potassium as well as in deficits of sodium and chloride. Diminished intake of potassium and losses of this ion in diarrheal stools produce considerable deficits of potassium, sodium, chloride, and water.[10] In addition to the losses of bicarbonate with sodium in the stools, the extracellular bicarbonate level is reduced by loss of bicarbonate with potassium in the stools. The cellular deficit of potassium is partially replaced with extracellular sodium. Similar changes in body composition occur in diabetic coma. Organic acids are excreted with potassium as well as with sodium. Although some of the reduction in plasma bicarbonate is accounted for by displacement of bicarbonate by ketone acids, a major part is usually caused by excretion of bicarbonate with sodium and potassium.

The importance of the changes in body composition is brought out in studies of experimental alkalosis with potassium deficiency in rats. The exchange of ions between extracellular and intracellular fluids, as well as by renal regulation, explains the restoration of normal acid-base equilibrium by administration of either potassium chloride or potassium bicarbonate with no external source of sodium.[7] With the administration of potassium chloride, the exchange between extracellular and intracellular fluids may be depicted as follows: 3 KCl is added to the extracellular fluids; 3 K^+ enter the cells in exchange for 2 Na^+ and 1 H^+. The H^+Cl^- reacts with $NaHCO_3$ to form CO^*, H^*O, and Na^+Cl^-. Consequently, bicarbonate concentration is restored without excretion of bicarbonate by the kidneys being required. With administration of potassium bicarbonate, the same exchange at the membrane takes place; 2 $NaHCO_3$ and 1 H_2CO_3 are formed in extracellular fluids. Bicarbonate must be excreted by the kidneys in order to restore normal acid-base equilibrium. Chloride concentration rises (despite no external source of chloride) because extracellular volume decreases, as indicated by a decrease in body weight.

The foregoing description of the exchange between extracellular fluids and muscle indicates that the reverse exchange occurs during the development of metabolic alkalosis. In other words, the muscle cells in metabolic alkalosis have received an excess of hydrogen ions that is as great as the deficit of hydrogen ions in extracellular fluids. The excess of hydrogen ions probably produces little change in cell pH since protons from the hydrogen ions would form undissociated weak acids or possibly weak bases from amino compounds. Potassium is apparently necessary for the renal compensation of metabolic alkalosis. This observation is confirmed in those patients with metabolic alkalosis who fail to respond to administration of saline solution unless potassium is also available.[11]

Metabolic acidosis has not been studied in similar detail; however, it is clear that large doses of sodium bicarbonate are required to restore bicarbonate concentration in metabolic acidosis, not because the deficits of sodium bicarbonate are this great in extracellular fluid but because, as the result of a potassium

deficiency, a large part of the injected sodium ion enters the cells in exchange for the hydrogen ion. Since the extent of this transfer cannot be predicted in patients, the calculation of the dose of sodium bicarbonate required to restore acid-base equilibrium has no sound physiological basis. The cellular deficit of cations should be replaced with potassium. In general, acidosis accompanied by dehydration should be treated by replacing extracellular water and electrolytes by a solution resembling extracellular fluids, such as Hartmann's Ringer lactate. Simultaneously, or as soon as renal function and cellular metabolism are adequate, potassium should be given in amounts that adequately cover normal expenditure and replace some of the deficits. It is seldom necessary to give more bicarbonate than that contained in this solution; however, 4 mM. of sodium lactate per kilogram of body weight (25 ml. of 0.16 M) may safely be given in severe acidosis of this type.

Schwartz and Relman[12] have described persons with severe potassium deficiency that resulted from repeated use of cathartics. These patients did not develop alkalosis. The renal function was altered; hyposthenuria and moderate reduction in glomerular filtration were demonstrated. Renal function did not return entirely to normal over a period of several months. The authors postulated that prolonged potassium deficiency produces renal changes that are not rapidly reversed. The renal disturbances developing in some patients under prolonged Sippy treatment may be of this type.

Schwartz has reviewed the literature on potassium in relation to the kidneys.[13] The excretion of potassium increases when serum concentration of this ion increases. Both acidosis and alkalosis increase potassium excretion; administration of acetazolamide leads to prompt excretion of potassium. Urine with a high level of sodium usually has a high potassium level. The mercurial diuretics produce alkalosis that may or may not be accompanied by deficits of potassium. Desoxycorticosterone, aldosterone, cortisone and other corticosteroids, adrenotropic hormone, and activation of the adrenal cortex increase urinary potassium levels. When oliguria develops in renal failure or when extrarenal factors such as shock and dehydration are present, potassium tends to be retained and toxic levels may be reached. Nevertheless, potassium excretion is usually well maintained in advanced renal insufficiency as long as the urine volume is high. Indeed, symptoms of potassium deficiency have resulted from renal losses in some patients with hyposthenuric renal insufficiency.

The stools normally contain moderate amounts of potassium. Losses of potassium in patients with infantile diarrhea are as great as 17 mM. per day as compared to 2 mM. per day in healthy infants. Stool losses and decreased intake are largely responsible for potassium deficiency in diarrhea. In one study, stool concentration of potassium was reported to be about 57 mEq. per liter in fed patients; during the recovery of patients not fed, the potassium concentration in stools was about 40 mEq. per liter.[10] One patient with voluminous stools containing a large quantity of sodium and chloride was reported to be excreting only 6 mEq. of potassium per liter. When isotonic sodium chloride solution is placed in the colon, potassium concentration rises to about 40 mEq. per liter as sodium chloride and water are absorbed.[11] This finding suggests that the loss of potassium will be high if watery stools remain long in the colon but low if the fluids from the small intestine are rapidly passed through the colon. As was pointed out by Gamble,[14] death from diarrhea may be considered to result from accumulating deficits. It can be calculated that serious water deficits appear first when there is no replacement. If water is restored, deficits of sodium and chloride become serious after only a slightly longer period. If water, sodium, and chloride are restored, potassium deficits are serious after a slightly longer period.

Treatment of infantile diarrhea involves the restoration of water and electrolytes as well as the restoration of normal stools. In a report mentioned earlier, the average deficits were 125 gm. of water, 9 mM. of sodium chloride, and 12 mEq. of potassium per kilogram of body weight. A postacidotic state after the treatment of infantile diarrhea was described by Rapoport and associates.[15] A decrease in serum concentration of phosphorus, potassium, and calcium was frequent, and failure to recover was attributed to hypocalcemic tetany in many cases. Although I have observed hypocalcemia occasionally in patients recovering from infantile diarrhea, this finding has been rare when potassium as well as sodium salts have been used. A possible explanation of the contradictory experiences is that in normal rats administration of sodium chloride and sodium bicarbonate does not produce hypocalcemia, but the same salts reduce serum calcium concentration in rats previously depleted of potassium. Potassium deficiency alone does not reduce calcium concentration. It is believed that a disturbance in the regulation of extracellular calcium concentration develops when sodium concentration is rapidly increased in the presence of potassium deficiency. To the extent that hypocalcemia explains the postacidotic state, this hypothesis indicates that tetany of this type is an iatrogenic disorder resulting from the administration of too much sodium bicarbonate to patients deficient in potassium. Presumably, early administration of potassium prevents this disturbance.

The association of alkalosis and profuse watery stools in congenital alkalosis with diarrhea is a rare condition.[11] The fluid in the small intestines is normal and food is well absorbed; however, the stools contain large volumes of water, more chloride than sodium, and a considerable amount of potassium. The deficit of chloride accompanying marked elevation of the serum bicarbonate concentration is explained by stool losses, since the urine is practically devoid of chloride.

Prolonged fasting may induce marked alkalosis and potassium deficiency. Some patients with anorexia nervosa exhibit this phenomenon.

The treatment of potassium deficiency is essentially the same in persons of all ages. Deficits should be estimated in milliequivalents per kilogram of body weight and are unlikely to be greater than 17 mEq. per kilogram. It is usually safe to give 3 mEq. per kilogram per day together with the appropriate amounts of fluid to cover normal and abnormal expenditure and to restore initial deficits of sodium and chloride. The total fluid requirements in infants are sufficient so that this amount of potassium can be given at a concentration of 25 mEq. or less per liter. In adults, the appropriate amounts of fluid are such that concentration of potassium would have to be 60 mEq. per liter in order to supply this amount. It is desirable not to exceed a concentration of 40 mEq. per liter of fluid injected into the veins. The estimated amount of potassium for 24 hours may be injected more rapidly but not in less than 4 hours. For severe deficiency, somewhat larger doses may be given, but their effects should be carefully observed by electrocardiography, measurement of serum concentrations, and clinical observation of the patient. The amounts of potassium that can be given safely are such that it takes 4 to 6 days to replace large deficits.

Total fluid requirement should be estimated as 150 ml. per 100 calories metabolized. This practice takes into account the different rates of expenditure of water that accompany different metabolic rates in infants and adults and other factors altering total metabolism. Total metabolism is usually about 1,000 calories per square meter of body surface, and fluid requirement about 1,500 ml.; however, in newborn infants who have not been fed, the total metabolism is low—about 60% of the usual amount per square meter. The fluid requirement after operations in the newborn infant is not low per unit of metabolism. It is lower than the usual amounts calculated per kilogram of body weight or per unit of surface area.

The expenditure of potassium when all fluids are given parenterally varies from 1 to 3 mEq. per 100 calories metabolized—usually 20 to 30 mEq. per square meter per 24 hours. Even when there is no deficit of potassium, these amounts should be given in order to prevent deficiency.

A suitable mixture for replacement of fluid removed by gastric suction is sodium chloride solution of about one-half isotonic strength and 40 mM. of potassium chloride (3 gm.) per liter in a 2.5% dextrose solution. In most cases of metabolic alkalosis, the deficits of sodium chloride are replaced by 20 to 40 ml. per kilogram of isotonic sodium chloride solution. To this, the therapeutic amount of potassium chloride should be added.

Often electrolyte therapy can be oral when food cannot be taken. The requirements of water, sodium, chloride, and potassium are the same as when all fluids are given parenterally. This means that the normal expenditure of 3 mM. of sodium chloride and 2 mEq. of potassium per 100 calories metabolized would be given in 150 ml. of water. It is advisable to prescribe definite mixtures such as 1 gm. each of sodium chloride, sodium bicarbonate, and potassium chloride in a liter or quart of a 5% glucose solution. Such a solution has made it possible to handle practically all cases of mild infantile diarrhea without administering fluids parenterally. Use of the mixture permits the period of parenteral administration of fluid to be shortened. The solution has been useful in the postoperative care of infants and children and is appropriate in both acidosis and alkalosis; there is no reason why it should not be effective in similar conditions in adults. I have found it more convenient and safer to use a mixture of definite composition manufactured for this purpose (Lytren). This mixture contains electrolytes sufficient to replace moderate deficits of sodium, chloride, and potassium and to provide for a moderate increase in expenditure. Such mixtures should be prescribed in definite amounts suitable to cover normal water expenditure. Additional water may then be added when expenditure of water is high.

Summary

Potassium deficiency is likely to develop in acidosis or alkalosis when there is prolonged diarrhea or prolonged parenterally given fluid therapy without potassium. Fasting may induce deficiency. The cortical hormones increase the amount of potassium in the urine. Renal function is altered by alkalosis so that potassium deficiency is likely to appear. Potassium deficiency alters renal function so that alkalosis appears or persists. The excretion of loads of anions with potassium is part of the cause of potassium deficiency in acidosis. Potassium intoxication may develop when oliguria occurs in renal disease or when renal function is impaired by extrarenal factors such as shock or dehydration. Administration of potassium with suitable mixtures of sodium, chloride, and glucose in water is relatively safe if certain rules as to dose and rate of administration are followed. Renal function should be good and the circulatory failure of shock overcome. The chief contraindication to potassium therapy is renal failure with oliguria and untreated adrenal insufficiency.

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COUNCIL ON PHARMACY AND CHEMISTRY

NEW AND NONOFFICIAL REMEDIES

Monographs and supplemental statements on drugs described here and in subsequent editions of New and Nonofficial Remedies are based on the evaluation of available scientific data and reports of investigations. Applicable commercial names for preparations of evaluated drugs are listed at the end of monographs and parenthetically in the text of supplemental statements; additional commercial names of which the Council is informed will be included with subsequently published supplemental statements and annual editions of New and Nonofficial Remedies.

H. D. KAUTZ, M.D., *Secretary.*

Topical Use of Prednisolone

The Council has evaluated the topical use of prednisolone (Meti-Derm) for the local management of dermatoses susceptible to gluco-steroid therapy. On the basis of currently available evidence, the Council concluded that the drug, incorporated in a suitable dermatological vehicle, is effective in ameliorating cutaneous manifestations of acute and chronic dermatoses that have an allergic or inflammatory basis and are associated with pruritus. These include such conditions as contact dermatitis, various forms of atopic dermatitis, seborrheic dermatitis, nonspecific anogenital pruritus, and lichenified pruritus. No systemic side-effects have been observed after absorption of the drug. In some cases, sensitization or irritation may follow its topical application, particularly to an eroded skin; however, this is more likely to be caused by the base in which it is incorporated than by prednisolone itself. The drug should not be applied to infected areas of the skin.

For topical administration, a cream containing 5 mg. of prednisolone per gram is applied to the affected areas of the skin three or four times daily.

The Council voted to amend New and Nonofficial Remedies accordingly to describe the use of prednisolone by the topical route.

Schering Corporation cooperated by furnishing scientific data to aid in the evaluation of the topical use of prednisolone.

Intramuscular Use of Crystalline Trypsin

The Council has evaluated the intramuscular use of an oil suspension of crystalline trypsin (Parenzyme) for the treatment of thrombophlebitis, phlebothrombosis, ocular inflammations, traumatic wounds, and varicose and diabetic leg ulcers. Currently available evidence suggests that many patients respond favorably to the drug. While few controlled clinical studies have been published to date, other reports indicate that a majority of patients refractory to standard modalities obtain beneficial results from trypsin administered intramuscularly. It should not be given in lieu of anticoagulants but as adjunctive therapy for reduction of inflammation and edema at the site of phlebitic processes.

Crystalline trypsin in oil produces pain and induration at the site of intramuscular injection in a sizable proportion of patients; however, the incidence of these side-effects may be appreciably reduced if a thoroughly dry and sharp needle is employed. Febrile reactions and leukocytoses, resembling those produced by parenteral administration of foreign protein, are rare. Occasionally, angioneurotic edema, hives, and urticaria occur. The drug is contraindicated or should be used with extreme caution in patients with renal or hepatic damage, blood clotting abnormalities, or hemorrhagic states. Its ultimate safety after long-term intramuscular therapy is not as yet completely determined.

Crystalline trypsin in oil is administered by deep intragluteal injection, alternating sites and buttocks. Prior to administration, sensitization tests should be performed on patients with a history of hypersensitivity. Doses of 2.5 to 5 mg., one to four times daily for three to eight days, have been administered and should be considered tentative. Dosage must be individualized and depends on the severity of symptoms and the degree of response. Adequate precautions against accidental intravenous injections should be exercised.

The Council voted to amend New and Nonofficial Remedies accordingly to describe the intramuscular use of a suspension of crystalline trypsin in oil.

The National Drug Company cooperated by furnishing scientific data to aid in the evaluation of the intramuscular use of crystalline trypsin.

MEDICINE AT WORK

CHEER UP!
MORE HOSPITALS ARE SAYING SO

"If you are a maternity case you have an extremely healthy ailment. An old lady we know told her expecting granddaughters that the whole army and navy came that way."

•

"We use 146,000 clean diapers (a year)—to dry them at the same time we would need a 90-mile clothesline (stretching from Philadelphia to New York.)"

•

"A mechanic fixes machinery. A doctor fixes people . . . Some doctors have boys and girls of their own. Doctors love children and they work hard to make sick children well again."

•

"Lenox Hill is a nonprofit hospital . . . and, you will hardly believe it, in a way we are proud of losing money. It proves that we are not using a hospital bed as a milk cow."

•

(In answer to how many times a day a buzzer rings in the hospital): "3,000 times. Of course 398 times are on account of old Mrs. B. . . . who wages real push-button warfare against us."

Folksy comments like these are greeting millions of hospital patients every year in sprightly booklets liberally sprinkled with cartoons, photos, and artistic use of color. The frightened child facing an operation in New York City's Memorial Center relaxes in calm curiosity of "the x-ray camera that takes a picture of the inside of your body." The depressed tubercular in Philadelphia General Hospital cannot suppress a smile at the caricature in his booklet of two patients shooting dice beside coins and bills on the ward floor—under the caption: "Gambling is not permitted in the hospital."

Adorning the cover of the Palo Alto, Calif., Hospital's patient information booklet is a sketched physician-stork standing atop a chimney on one leg and peering at a watch held in the other. Inside the pamphlet is a series of questions and answers for expectant mothers. Sample: "Q. When do I see my husband again? A. After the nurses finish preparing you for delivery, he will be called from the Heir Port."

Booklet Success Is Spreading

This sort of light informative touch has been so successful in recent years that many hospital administrators, physicians, nurses, and patients find themselves wondering why it has not been done before on a large scale. The Franklin Square Hospital in Baltimore not long ago began distributing instructional sheets for the patient (one sheet prepares him for a basal metabolism test—under the sketch of a sprawling hound and the heading: "Let's see how lazy YOU can be").

Hospital Administrator Sanford Kotzen questioned doctors who had enjoyed privileges at several hospitals—to verify that the patient information sheets were eliminating interruptions in preoperative and prediagnostic routine. One physician told Kotzen: "This is the kind of thing hospitals should have done long ago." Another said: "They should have something like these in all hospitals."

Already, the American Hospital Association notes "an increasing interest" among the nation's 7,000 hospitals in publishing informational material for the 21 million patients who go through their doors each year. At last report, 26% of the hospitals were offering this service—ranging from 11% of the proprietary general and special short-term hospitals to 50% of all tuberculosis hospitals in the United States. Now, says the A. H. A., "patients' booklets are used regularly more than any other" hospital publications, including employe information sheets, house organs, and annual reports.

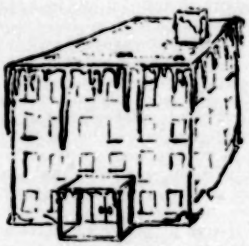
Not long ago in a survey, the nearly 2,000 hospitals that publish information for patients were asked to report response to their booklets. Not one comment was unfavorable. The praises included: "Patients like it and doctors feel it helps the patient understand," and "a very valuable technique in the rapid orientation of the patient." All agreed that the price of publication was well worth the long-run public relations and immediate-cooperation value received.

Examples of effective booklets range from a two-fold sheet costing less than a penny a copy (and containing hospital rules, visitors hours, rates, cost of guest meals, and list of staff members and credentials) to a 30-page slick pamphlet with pictures and color, costing 12½ cents a copy (and carrying complete information about the hospital with line drawings on each page). Says the A. H. A.: "There is no reason why an economy-minded administration could not mimeograph essential information in a neat and readable form."

Cold Versus Warm Treatment

For years, many a doctor has been concerned with how conditions in a few "cold" hospitals have chilled tensely his otherwise warm patients at a crucial time

when preoperational relaxation is so important. The physician knows that when a hospital informs his patients of the things and routine around them, and what is happening to them and why, the resulting cooperation makes for better convalescence and often a shorter stay in the hospital. At the same time, the hush-hush of the medieval medical approach is eliminated by dispelling a sometimes popular notion that medicine lies in a realm of deep dark secrets.



The 32-page illustrated handbook for patients in the new Hunterdon Medical Center in Flemington, N. J., stresses medical care as "a team problem, too complicated for any single physician to provide." That note is echoed by the University Hospital at Ann Arbor, Mich., in a booklet that lists the many hospital people who contribute to the patient's comforts.

The booklet of Boston's Peter Bent Brigham Hospital carries this reminder: "Mr. Patient sees the doctor, the nurse, the food he does not want, the early morning call, the cashier to whom he pays his bills." Then, taking the opportunity to show what today's sharply higher hospital bills are paying for, the booklet continues: "But he does not see the pharmacist, the sterile supply room, the medical record library, the instrument repair shop, the surgical supply room . . . the operating room and its costly equipment . . . the expert radiologist . . . the blood bank . . . the costly laboratory equipment and the trained personnel . . . the dietary department and the gleaming modern kitchens . . . the laundry . . . the linen and supply rooms . . . the elaborate power plant . . . the window cleaner, the refrigeration mechanic, the steam-fitter, the plumber, the carpenter, the painter, the elevator mechanic . . ."

There is greater cooperation when the patient understands what rules in the book he is expected to follow. Nurses have an easier time of it because many questions they would be asked are answered in print. All this conditioning expands the doctor-patient atmosphere of confidence and cordiality so essential to medical counseling.

Information booklets are kept in some doctors' offices so that the prospective patient can prepare for a hospital stay. This is particularly effective in maternity cases. The Presbyterian Hospital in Chicago puts out a 32-page booklet that is fine art with its gently stylized sketches of mother and child and with its easily understood advisory text covering suggested diets and also conditions before, during, and after birth. (At one point, it is stated in the booklet: "At no time are you to substitute this booklet or any other for your doctor. Nothing can take the place of the careful supervision you will receive from your physician.")

Personal Approach Does It

Most of the pamphlets are written with the personal approach. The Medical College of Virginia Hospital in Richmond asks its patients to grade the hospital in a back-page quiz on food, services, and suggestions for improvement. The University (of Michigan) Hospital tells its story in the words of a "typical" woman patient facing problems and questions encountered by any patient. Dr. Jack Weatherly, as staff psychiatrist in the Veterans Administration Hospital at Gulfport, Miss., writes that the psychiatric patient often responds favorably to the use of personal pronouns in the booklet text: "You will be seen soon by your ward doctor and, later, when your own case doctor sees you, you can spend as much time as you need to talk over your problem."

"The pen is mightier than the scalpel," says the A. H. A. in urging more hospitals to publish information for patients. The association recommends that the writing be done by people who have the same fears, confusion, and anxiety as patients—if possible, by people not in the hospital field. They say this advice has brought about the current crop of humor, lighthearted copy, and touching line drawings among the booklets being published today in the U. S. (A straightforward approach is used for psychiatric patients, since they might easily misconstrue efforts at wit and cheery pep talks.)

You can still become a patient in a hospital that is devoid of the personal touch. At some places, you can still gaze through the institutional atmosphere at things and people sterile and antiseptic—only occasionally seeing also your own physician as personification of familiar warmth and understanding. But today, as never before, you will find this picture of hospital life diminishing in the United States. Many physicians would like to see it vanish completely.

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VIRAL ETIOLOGY OF CANCER AND LEUKEMIA?

GUEST EDITORIAL

Ludwik Gross, M.D.

Chief, Cancer Research Unit, Veterans Administration Hospital, Bronx 68, N. Y.

During the past decade the concept of viral etiology of cancer and allied diseases has gained considerable momentum. Experimental data began to accumulate pointing more and more to the possibility that many, if not all, malignant tumors may be caused by viruses. Thus, a large number of malignant tumors of different morphology and in different species of animals could be transmitted from one host to another by filtered extracts. At this time, most of the common tumors in chickens, such as the various forms of leukemia and sarcoma, have been found to be transmitted by filtered extracts. The natural epidemiology of chicken lymphomatosis through the embryonated eggs has also been established.[1] In some instances, among newly hatched chicks, the transmission may be air-borne.

The most impressive recent advances, however, in the field of viral etiology of tumors have been accomplished in mice. The fundamental discovery of Bittner[2] in 1936, showing that a certain form of breast carcinoma in the mouse is due to a virus that is transmitted in the milk from healthy (at the time of transmission) carrier mothers to their suckling offspring, could be considered the turning point in the history of modern cancer research. Fifteen years later, in 1951, mouse leukemia, a disease clinically and morphologically strikingly similar to that occurring in humans, was demonstrated[3] to be caused by a filterable virus. The use of newborn animals proved to be essential for successful transmission of the cell-free leukemic agent in mice. Shortly afterward it was found[4] that, when filtered extracts prepared from leukemic mice were inoculated into newborn animals of certain susceptible nonleukemic strains, some animals developed leukemia, whereas others developed parotid gland carcinomas and/or subcutaneous fibromyxosarcomas. These results have been recently confirmed by Woolley,[5] at the Sloan-Kettering Institute in New York. When, later, filtered extracts were prepared from parotid tumors, or sarcomas, and inoculated into newborn mice, either leukemia, or parotid tumors, and/or subcutaneous sarcomas developed. Similarly, when Graffi and co-workers[6] in Germany inoculated filtered extracts prepared from a transplanted mouse mammary carcinoma into newborn mice, a high percentage of the injected animals developed typical generalized leukemia. The question immediately arose whether one single virus may be able to induce leukemia, parotid gland tumors, subcutaneous sarcomas, or carcinomas, or whether the leukemic extracts contained a mixture of distinct, though possibly related, oncogenic agents. This question, which is of fundamental importance, has not yet been answered.

In further experiments it was demonstrated[7] that carrier mice of leukemic strains, earmarked to develop leukemia at middle age, even though in apparent good health when young, transmit the virus to their offspring. This transmission occurs not through the milk, as in the case of mammary carcinoma, but directly through the embryos, from one generation to another. Mouse leukemia, as chicken lymphomatosis, appears to be, therefore, an egg-borne virus disease. In more recent studies it has been shown that the mouse leukemia virus is a spherical particle less than 70 m μ in diameter, which can be visualized in an electron microscope,[7] and that this agent is present in various organs of the carrier animals, and in leukemic tumors and blood plasma of leukemic mice.

In all these experiments, it was necessary to inject newborn mice, only a few hours old, in order to induce, with cell-free extracts, leukemia, parotid gland tumors, or sarcomas. It appeared, therefore, that the use of an animal not more than a few hours old was essential for the successful transmission of these oncogenic agents. When, however, Friend,[8] at the Sloan-Kettering Institute in New York, inoculated cell-free extracts, prepared from a transplanted Ehrlich ascites mouse carcinoma, into newborn Swiss mice, some of the inoculated mice developed generalized leukemia 14 months later; one of these leukemias, a myelogenous form, proved to be transmissible by filtered extracts into adult Swiss mice.

There may exist, therefore, different mouse leukemia viruses, some transmissible to newborn hosts only, others to adult hosts as well. Beard[9] and his associates

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5. Woolley, G. W., and Small, M. C.: Experiments on Cell-Free Transmission of Mouse Leukemia, Cancer **9**: 1102-1108 (Nov.-Dec.) 1956.
6. Graffi, A.; Bielka, H., and Fey, F.: Leukämieerzeugung durch ein filtrierbares Agens aus malignen Tumoren, Acta haemat. **15**: 145-174 (March) 1956.
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8. Friend, C.: Isolation of Virus Causing Malignant Disease of Hematopoietic System in Adult Swiss Mice, abstracted, Proc. Am. A. Cancer Res. **2**: 108 (April) 1956.
9. Beard, J. W.: Virus of Avian Myeloblastic Leukosis, Poultry Sci. **35**: 305-323 (Jan.) 1956. Eckert, E. A.; Beard, D., and Beard, J. W.: Virus of Avian Erythroblastosis. I. Titration of Infectivity, J. Nat. Cancer Inst. **16**: 1099-1120 (April) 1956.

at Duke University made similar observations in their studies on chicken leukemia: whereas chicks less than 3 days old had to be used for inoculation with the myeloblastosis virus, young adult chickens could be inoculated with the virus of erythroblastosis. Although these two viruses are indistinguishable in electron micrographs, representing spherical particles about 120 m μ in diameter, they induce distinct forms of chicken leukemia.[9]

These recent developments in experimental cancer research add significantly to the older experiments in which various tumors in chickens, rabbits, frogs, and mice have been transmitted by filtered extracts. In humans thus far only warts and papillomas have been found to be transmissible by filtered extracts. By analogy, however, it is quite apparent that many other human tumors may be caused by viruses. It is entirely possible that most, if not all, malignant tumors, not only in animals but also in humans, are caused by filterable viruses. Many of these viruses may be transmitted from generation to generation,[7] remaining in a latent form harmless for their carrier hosts. Now and then, however, prompted by some obscure activating factors (some of them physiological, such as metabolic or hormonal, others extrinsic, such as chemical poisons or ionizing radiation), these hitherto dormant viruses may change into tumor-producing pathogens. Such "accidents" may happen only occasionally, separated by several generations of healthy carriers.[7]

Should this concept prove to be true, oncogenic viruses could be compared to temperate bacteriophages, transmitted from one generation to another in lysogenic bacterial hosts, only very occasionally killing some of their carriers. This concept would throw a different light on the carcinogenic action of certain chemicals as well as the development of leukemia in radiologists and in population groups exposed to ionizing radiation. It would also explain the striking, though rare, reports of familial incidence of cancer and leukemia in humans.

ANNUAL CONGRESS ON MEDICAL EDUCATION AND LICENSURE

At the Congress on Medical Education and Licensure scheduled to be held at the Palmer House, Chicago, February 10-12, 1957, the Council on Medical Education is planning its program to deal with current problems of widespread interest in medical education.

The program on Sunday morning, February 10, will be devoted to a conference on Graduate Medical Education for General Practice—1957, which will be cosponsored by the Advisory Board for Medical Specialties and the Council. This conference will be introduced by two background statements, one presenting the role of undergraduate medical education today and the other presenting the concept of general practice regarding adequate graduate medical education in preparation for general practice—1957. These two background papers will be followed by a series of short, clean-cut presentations of what should constitute graduate medical education for general practice today as seen from the point of view of (*a*) internal medicine, (*b*) pediatrics, (*c*) surgery, (*d*) obstetrics and gynecology, and (*e*) psychiatry. Ample time will be permitted after these presentations for discussion from the floor, with the speakers acting as a panel. It is hoped that this conference will aid in better clarification of the graduate needs in preparation for general practice—1957, rather than their interpretation in the setting of some years ago. This should be an interesting and valuable conference for all concerned with internship and residency training programs in both specialty and general practice.

Sunday afternoon, February 10, will be devoted to the regular business meetings of the Advisory Board for Medical Specialties and the Federation of State Medical Boards of the United States.

Monday, February 11, will be devoted to a symposium on Medical Education Tomorrow during the morning session. The introductory paper will deal with the "lasting values in medical education" as opposed to the more transitory or temporary values. In projecting the discussion of Medical Education Tomorrow, papers will be presented on medical education as a cultural experience, the importance of and concern over natural and physical sciences remaining basic in the education of the physician, the need for structuring medical education to adequately reflect medical research in both knowledge and attitudes, and the "pros and cons" of interpretation and correlation. Efforts will be made to deal with the factors that are most important in creating the current unrest among medical educators in the search for new and better objectives, as well as techniques and methodologies.

The afternoon session on February 11 will focus attention on Postgraduate Medical Education. The keynote of this session will deal with the importance and challenges presented by this field. This will be followed by a presentation of the development of medical school–state medical society postgraduate programs (an analysis of the Kansas story). The role of a community hospital in continuing education will be highlighted by the Hunterdoon experiment and the potential significance of its general pattern to postgraduate medical education. The regional-hospital-medical school affiliation potentialities as exemplified by such programs as the Michigan Plan and the New York University Plan will also be presented. This program should also be of high interest to hospital administrators, state and local medical societies, and directors of postgraduate programs of medical education as well as to medical school administrators and faculty personnel.

The Federation of State Medical Boards of the United States will hold their Annual Federation Banquet on Monday evening, February 11. On Tuesday, February 12, the Federation will conduct its annual program around the general theme of "Re-evaluation of the Licensing Examination." This challenging area of concern should be of interest to those engaged in the various aspects of undergraduate and graduate medical education as well as to those concerned with licensure.

MEDICAL NEWS

CALIFORNIA

Society News.—The Los Angeles Physicians' Art Society has elected Dr. Douglas D. McKinnon, president; Dr. Alonzo B. Cass, president-elect; and Dr. Victor M. Marshall, secretary-treasurer. Dr. Samuel P. Danno, this year's winner, received the society's rotating "Oscar" from Dr. William M. Nethery, Glendale.

Physicist to Address Cardiac Conference.—The Cardiac Surgical Conference at Mount Zion Hospital, San Francisco, will be addressed by Norbert Wiener, Ph.D., who will speak at 10:15 a. m. Dec. 1 in Herbst Hall on "Use of the Ballistocardiogram as Evidence of Vascular Dynamics." Dr. Wiener is professor of physics at Massachusetts Institute of Technology in Cambridge.

Personal.—Dr. John R. Upton, assistant clinical professor of obstetrics and gynecology, University of California Medical School, Berkeley–San Francisco, has been appointed by Queen Elizabeth II as an associate officer in the Order of St. John for "his pioneer work in blood banking and his service to the British Commonwealth of Nations." This order of chivalry, which is over 900 years old, discarded its military status in 1888 and became a purely service organization.

CONNECTICUT

Course on Economics of Medical Practice.—The Connecticut State Medical Society, in cooperation with Yale University School of Medicine, New Haven, department of public health, is sponsoring a course on the economics and relationships of medical practice at the Brady Auditorium, 310 Cedar St., New Haven. At 8 p. m., Dec. 5, a special lecture, "Role of the Physician in Preventive Medicine," will be delivered by Dr. Dwight H. Murray, Napa, Calif., President, American Medical Association. On Dec. 13, the series on "Careers in Medicine" will be continued with a discussion on surgery by Drs. Edward J. Ottenheimer, Willimantic, and William H. Curley Jr., Bridgeport.

FLORIDA

Medical Society Honors First Graduating Class.—At a pregraduation dinner sponsored by the faculty of the first graduating class of the University of Miami School of Medicine, Coral Gables, the Dade County Medical Association presented an engraved plaque bearing the English translation of the oath of Hippocrates. A brass plate below the engraving is inscribed: "Presented to the University of Miami School of Medicine in honor of its first graduating class June 11, 1956 by the Dade County Medical Association. Hunter B. Rogers, President, Vincent P. Corso, Secretary." Dr. Rogers was invited by Homer F. Marsh, Ph.D., professor of bacteriology and dean of the medical school, to administer the oath to the new physicians.

ILLINOIS

Lecture in Winnetka.—Dr. Lauretta Bender, professor of clinical psychiatry, New York University College of Medicine, and principal research scientist in child psychiatry, New York State Department of Mental Hygiene, will present "Problems of Early Development" Dec. 5, 8 p. m., at the North Shore Health Resort, 225 Sheridan Rd., Winnetka. Physicians are invited.

Meeting on Physical Medicine.—The Chicago Society of Physical Medicine and Rehabilitation will hold its regular meeting Dec. 1, 2 p. m., at the Institute of Physical Medicine and Rehabilitation, 619 N. Glen Oak Ave., Peoria. The program, "The Physiatrist and the Patient's Physician," will be presented by the medical staff, Institute of Physical Medicine and Rehabilitation, and representative members of the medical staffs of St. Francis Hospital and the Methodist Hospital of Central Illinois. At 3 p. m. there will be a tour of the institute. A social hour, 5 p. m., will precede dinner.

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

Chicago

Lectures on History of Surgery.—The International College of Surgeons is sponsoring a series of lectures on the history of surgery at the Surgeons' Hall of Fame, 1524 Lake Shore Dr. All physicians will be welcome to attend. On Dec. 4, "The Middle Ages in Medicine and the School of Salerno" will be considered by Mr. Loren MacKenney, professor of history, University of North Carolina, Chapel Hill.

Society News.—The Institute of Medicine of Chicago will hold its 41st annual meeting Dec. 4 at the Furniture Club of America, 17th floor, 667 N. McClurg Ct. (telephone during the meeting: WHitehall 4-8552). The open meeting at 8 p. m. will be preceded by the annual reception, 6 p. m., and dinner, 7 p. m., for fellows of the institute, their wives, and other guests. The presidential address, "The Medical Outlook from Washington, D. C.," will be delivered at 9 p. m. by Dr. Lowell T. Coggeshall.

Symposium on Parenteral Therapy with Fluids.—A symposium on parenteral therapy with fluids, co-sponsored by the Chicago Medical Society and Baxter Laboratories, Inc., will be held at the Sheraton Hotel, Dec. 5-6, in connection with the 25th anniversary of Baxter Laboratories and pioneering by Chicago physicians in the development of such therapy. All physicians are invited to attend. There is no registration fee. The program, which will open with a review of the development of parenteral therapy with fluids by Dr. Karl A. Meyer, president, Chicago Medical Society, will include the following presentations:

Physiology of Acid Base Balance, Harry F. Weisberg, Chicago.
Diagnosis of Fluid Electrolyte Imbalance, Harvey R. Bernard, St. Louis.
Third Body Space—Translocation of Fluid, Parker Vanamee, New York City.
Special Pediatric Problems, Charles U. Lowe, Buffalo.
Therapy of Fluid Electrolyte Problems, Carl O. Rice, Minneapolis.
Use of Blood, Ralph M. Hartwell, New Orleans.
Use of Plasma Volume Expanders, Jacob J. Weinstein, Washington, D. C.
Treatment of Burns, Major Bruce G. MacMillan, M.C., Brooke Army Medical Center, Fort Sam Houston, Texas.
Carbohydrates, Rachmiel Levine, Chicago.
Vitamins, Tom D. Spies, Birmingham.
Protein, William E. Abbott, Cleveland.
Fat, Frederick J. Stare, Boston.

IOWA

Tumor Conference.—The Iowa division, American Cancer Society, and the University Hospitals, State University of Iowa College of Medicine, Iowa City, will present a tumor conference Dec. 7-8. A symposium on leukemias and lymphomas will be conducted at 11 a. m. Friday, by Drs. Willis M. Fowler, John R. Carter, and Higdon B. Elkins. "Viruses and Cancer" by Dr. Richard E. Shope, Rockefeller Hospital for Medical Research, New York City, will be presented at 4:10 p. m. Friday, and a lecture on bone cancer, with special reference to cartilaginous tumors, will be given at 11 a. m. Saturday, by Dr. Granville A. Bennett, professor of pathology, University of Illinois College of Medicine, Chicago. The program will also include the following presentations by Iowa City participants:

Gynecologic Cancer—Helpful Hints in Diagnosis, William C. Krettel.
What Therapy Can Do for Female Pelvic Cancer, John H. Randall.
Cancer of the Breast: A Quarter Century at University Hospitals, Robert C. Hickey.
Palliation of Advanced Breast Cancer, Robert T. Tidrick.
The Pediatrician Discovers a Mass—What Then? John D. MacQueen.
The Surgeon and the Child with Cancer, John A. Gius.
Urological Diagnostic Hints, Raymond G. Bunge.
Recent Changes in Therapy of Cancer of the Gastrointestinal Tract, Rubin Flocks.
The Place of Isotopes in Cancer Care: Present and Future Potentials, Titus Evans, Ph.D.
Lesions Produced by Aminonitriles, Ignacio V. Pometi.
Dermatologist and Cutaneous Cancers, Ruben Nomland.
Special Problems in Cutaneous Cancer for the Surgeon, Sidney E. Ziffren.
Shadow in the Lung—the Internist, Paul M. Seebohm.
Shadow in the Lung—the Surgeon, Johann L. Ehrenhaft.

Dr. Marc Hollender Goes to Syracuse.—Dr. Marc H. Hollender, associate professor of psychiatry, University of Illinois College of Medicine, and staff member of the Institute for Psychoanalysis, has been appointed professor and chairman of the department of psychiatry at State University of New York College of Medicine at Syracuse. Dr. Hollender succeeds Dr. Edward J. Stainbrook, who resigned last February to become professor and chairman of psychiatry at the University of Southern California, Los Angeles, and chief of psychiatric services at Los Angeles County Hospital. Dr. Hollender has been affiliated with Cook County Hospital and the University of Illinois Neuropsychiatric Institute. From 1942 to 1946 he served in the Air Force Medical Corps. In 1949 he received certification in psychiatry from the American Board of Psychiatry and Neurology.

MASSACHUSETTS

Dr. Hume Goes to Virginia.—Dr. David M. Hume, assistant professor of surgery and director of surgical research at the Harvard Medical School, Boston, has been appointed professor of surgery at the Medical College of Virginia, Richmond, to succeed the late Dr. Isaac A. Bigger. He assumed his duties as professor and head of the department of surgery on Aug. 16.

Dr. Lennox Honored.—Dr. William G. Lennox, associate professor emeritus in neurology at Harvard Medical School, Boston, has been chosen by the American Pharmaceutical Manufacturers' Association as the recipient of its scientific award for his research on the adaption of psychotherapeutic agents in the treatment of mental diseases. Dr. Lennox is a past-president of the International League Against Epilepsy and a founder of the American Epilepsy League. The presentation to Dr. Lennox will be made at the mid-year meeting of the association, Dec. 11 at the Waldorf-Astoria Hotel in New York City.

Dr. Solomon Becomes Emeritus Professor.—Dr. Harry C. Solomon, Boston, who helped to shape the early development of the teaching of psychiatry in the Harvard Medical School, has become emeritus professor of psychiatry, but will continue as medical director and superintendent of the Boston Psychopathic Hospital, the major center for the teaching of psychiatry in the medical school. He is currently president-elect of the American Psychiatric Association and president of the Association for Research in Nervous and Mental Disease. Dr. Solomon served as a first lieutenant with the Army Medical Corps in 1918-1919 and during World War II was chief neuropsychiatric examiner of the Boston Recruiting and Induction Station and a consultant to the Secretary of War. Among his many scientific publications are "Syphilis of the Innocent," "Studies in Lobotomy," "Neurosyphilis," "The Frontal Lobes and Schizophrenia," and "Manual of Neuropsychiatry," of which he was co-editor.

MICHIGAN

Symposium on Trauma.—The fifth annual Symposium on Trauma, sponsored by the Wayne State University Medical School, Detroit, and the Michigan Regional Committee on Trauma, will be held Dec. 5. Exhibits will be shown in the morning at the Farwell Building. A complimentary luncheon sponsored by the Upjohn Company will be given in the Medical School Cafeteria. The presentation of Dr. Henry C. Marble, Boston, the afternoon guest speaker, will be followed by two panel discussions in the auditorium of the Lafayette Clinic. Registration fee is $2. Interns and residents will be admitted free.

NEW JERSEY

Doctors' Chorus Aids Chronically Ill.—The doctors' chorus of the Essex County Medical Society recently presented to the Essex County service for the chronically ill $1,300, the net proceeds of the 1958 benefit concert, bringing to $11,500 its contributions to this service. The chorus closed its 1955-1958 season with the third benefit concert for the Roseville Y.M.C.A.

Visiting Chiefs at Hospital.—The Atlantic City Hospital will have as visiting chiefs pro-tem Dr. Bernard Fisher, assistant professor of surgery, University of Pittsburgh School of Medicine, Dec. 3-7; Dr. William T. Fitts Jr., associate professor of surgery, University of Pennsylvania School of Medicine, Philadelphia, Dec. 10-14; Dr. S. Leon Israel, associate professor of obstetrics and gynecology, University of Pennsylvania Graduate School of Medicine, Philadelphia, Dec. 17-19; Dr. Charles W. Charny, associate in urology, Hahnemann Medical College and Hospital of Philadelphia, Dec. 20-21.

Tumor Seminar.—The sixth annual slide seminar on "Unusual Tumors," sponsored by the New Jersey Society of Clinical Pathologists and the New Jersey State Department of Health, bureau of pathology, will be held at 2 p. m., Dec. 8, in the Essex House, Clinton and Broad streets, Newark. The moderator will be Dr. Arthur P. Stout, Institute for Cancer Research, Columbia University College of Physicians and Surgeons. All physicians are welcome. A social hour and dinner, with Dr. Stout as guest, will be held at the Essex House after the seminar. Reservations for the dinner may be made through Dr. Murray W. Shulman, Irvington General Hospital, Irvington, chairman of the seminar.

Annual Martland Lecture.—The Essex County Pathological and Anatomical Society will present the 20th annual Harrison S. Martland Lecture, Dec. 5, at the Academy of Medicine, 91 Lincoln Pk., Newark. Dr. Sidney Farber, professor of pathology, Harvard Medical School, and director of the Cancer Research Foundation at the Children's Hospital Center, Boston, will discuss "Progress in the Treatment and Control of Cancer." The meeting, which will be held in conjunction with the Academy of Medicine of New Jersey and the Essex County Medical Society, will be preceded by dinner at the Essex House Hotel, Broad Street. Reservations, $5 per person, should be sent to Dr. Murray W. Shulman, 913 20th St., Newark 8. All members of the profession are invited.

NEW MEXICO

Society News.—The New Mexico Medical Society has appointed Dr. Aaron E. Margulis, Santa Fe, as its state scientific editor and member of the *Rocky Mountain Medical Journal* editorial board, to succeed Dr. Carl H. Gellenthien, Valmora, who retired from the editorship after almost 12 years of service.

NEW YORK

Lecture in Gerontology.—Dr. Edmund V. Cowdry, director of the division of cancer research, Washington University School of Medicine, St. Louis, will deliver the third annual Lecture in Gerontology at the Hospital Division, Brooklyn Hebrew Home & Hospital for the Aged, 813 Howard Ave., Brooklyn, Dec. 6, 8:30 p. m.

Assembly on Anesthesiology.—The 10th Postgraduate Assembly of the New York State Society of Anesthesiologists at the Hotel New Yorker, New York City, Dec. 5-8, will open Wednesday at 9:30 a. m. with simultaneous panels on "Blood Transfusions: Problems, Results, Medicolegal Responsibilities" and "Current Trends in the Study of Kidney Function." Out-of-state participants in the former panel include C. Joseph Stetler, LL.M., director, Law Department, American Medical Association, Chicago, and Dr. William G. Workman, Bethesda, Md.; in the latter, Drs. Frederic C. Bartter, Bethesda, Md., and Joseph E. Murray, Boston. After roundtable luncheons at 12:30 p. m., panels will be presented on "Light Anesthesia, Balanced Anesthesia, or Polypharmacy" and "Circulatory Stress." Out-of-state participants in the former will include Drs. C. Ronald Stephen, Durham, N. C., and Philip D. Woodbridge, Greenfield, Mass.; and in the latter, Dr. Howard A. Frank, Boston. On Thursday afternoon, there will be a closed circuit telecast. The New York State Society of Anesthesiologists will be hosts at the annual cocktail party (7 p. m.) and dinner-dance (8 p. m.), honoring Dr. Emory A. Rovenstine, New York City. Friday morning Dr. Robert M. Smith, Boston, will serve as chairman on a panel, "Management of the Infant for Surgery," in which the participants will be Drs. C. Everett Koop, Philadelphia; William O. McQuiston, Peoria, Ill.; and Earle L. Wrenn Jr., Memphis, Tenn. Simultaneously, Dr. James E. Eckenhoff, Philadelphia, will be chairman of a panel on antidotes in anesthesiology, with the following collaborators: Dr. John Adriani, New Orleans;

Edwin I. deBeer, Ph.D., Tuckahoe, New York, and Dr. Abraham Wikler, Lexington, Ky. Friday afternoon will be devoted to the Emory A. Rovenstine, M.D., Testimonial Scientific Program, and Saturday morning to the Resident's Program.

New York City

Wechsler Lecture.—The annual Israel S. Wechsler Lecture will be given Dec. 14, 8:30 p. m. at the Mount Sinai Hospital by Horace W. Magoun, Ph.D., professor of anatomy, University of California at Los Angeles School of Medicine. His subject will be "Aristotelian Psychology and the Twentieth Century Brain."

Conference on Cardiac Disease.—The New York Heart Association will hold a one-day conference on "Atherosclerosis and Coronary Heart Disease" at the Waldorf-Astoria, Jan. 15, 1957. Speakers will include Drs. Paul D. White, Boston; Edwin C. Andrus, Baltimore; Herman E. Hilleboe, Albany, N. Y.; and Ancel B. Keys, Ph.D., Minneapolis.

Lecture on Neoplastic Diseases.—In a series of lectures on neoplastic diseases, Montefiore Hospital will offer "Studies of Interference with the Utilization of Precursors of Nucleic Acids" by Dr. Arnold D. Welch, chairman, department of pharmacology, Yale University School of Medicine, New Haven, Conn., Dec. 7 at 3 p. m. in the West Basement Conference Hall.

Howard Taylor Ricketts Award.—Dr. John C. Bugher, director of medical education and public health, Rockefeller Foundation, received the Howard Taylor Ricketts award for 1956 at a ceremony at the University of Chicago when Dr. Bugher read a paper on "Changing Patterns in the Public Health." The Howard Taylor Ricketts award was established by Mrs. Howard T. Ricketts after the death of her husband, a member of the Rush Medical College staff who discovered the cause of Rocky Mountain spotted fever and died on May 3, 1910, while doing research on typhus in Mexico City.

Symposium on Obesity.—The ninth A. Walter Suiter Lecture will be presented as a symposium on obesity at a meeting of the New York Academy of Medicine, 8:30 p. m. Dec. 6. The metabolic aspect of obesity will be discussed by Jean Mayer, Ph.D., associate professor of nutrition, Harvard School of Public Health, Boston; the neurophysiological aspect by Dr. John R. Brobeck, professor of physiology, University of Pennsylvania School of Medicine, Philadelphia; and the psychological aspects by Dr. Walter W. Hamburger, associate professor of psychiatry, University of Rochester School of Medicine and Dentistry. Although the symposium is intended primarily for physicians and public health workers, the public is invited to attend.

Schoenberg Memorial Program.—The 10th annual Schoenberg Memorial program of the New York Society for Clinical Ophthalmology and the National Society for the Prevention of Blindness will be held at the New York Academy of Medicine, Dec. 10, 8:15 p. m. The program honors the late Dr. Mark J. Schoenberg, a founder of the New York Society for Clinical Ophthalmology and first chairman of the committee on glaucoma of the national society. Dr. Irving H. Leopold, head, department of ophthalmology, University of Pennsylvania Graduate School of Medicine, Philadelphia, will speak on "Advances in the Medical Therapy of Glaucoma," and Dr. Hans Goldmann of the University of Berne, Switzerland, will discuss "The Problem of Glaucoma in Myopia." All physicians are invited.

OKLAHOMA

Cancer Conference.—The Oklahoma division of the American Cancer Society will hold its annual meeting in the auditorium of the University of Oklahoma School of Medicine, Oklahoma City, Dec. 8. The following out-of-state physicians will be among the guest speakers: Drs. Roger A. Harvey, head, department of radiology, University of Illinois College of Medicine, Chicago; Hayes Martin, associate professor of clinical surgery, Cornell University Medical College, New York; John R. Schenken, professor of pathology and bacteriology, University of Nebraska College of Medicine, Omaha; and Richard W. TeLinde, professor of gynecology, Johns Hopkins University School of Medicine, Baltimore.

PENNSYLVANIA

Philadelphia

Dr. Ravdin Retires from Army Reserve Corps.—Dr. Isador S. Ravdin, the John Rhea Barton Professor of Surgery at the University of Pennsylvania School of Medicine, was retired from service in the U. S. Army Medical Corps Reserve, Oct. 30. The ceremonies at the university were attended by ranking officers from Philadelphia; Washington, D. C.; and the Second Army Headquarters, Fort George G. Meade, Md. Gaylord P. Harnwell, LL.D., president of the university, was a speaker. Dr. Ravdin is the first medical officer to reach the rank of major general in the Army Reserve Corps. He received the Legion of Merit with oak leaf cluster for service as commander of the 20th General Hospital in Assam, India, during World War II, and also the Order of the Cloud and Banner, first degree, from China for this service. Brig. Gen. Harold G. Scheie, professor of ophthalmology and U. S. Army Reserve commanding general, 31st Hospital Center Reserve unit, Schuylkill Barracks, Philadelphia, presided. The U. S. Army field band played for this program. Dr. Ravdin is also director of the Harrison department of surgical research at the university, senior consultant to the Army surgeon general, a member of the Advisory Council on Health and Medicine, Office of the Secretary of Defense, and a member of the National Advisory Cancer Council to the surgeon general of the U. S. Public Health Service. He is a native of Indiana, the son, grandson, and great-grandson of physicians.

RHODE ISLAND

Hospital News.—The Rhode Island Hospital House Officers Alumni Association was recently organized. The following officers were elected: president, Dr. Russell B. Scobie, Newburgh, N. Y.; vice-president, Dr. J. Murray Beardsley, Providence; and secretary, Dr. Henry F. McCusker, Providence. The number of living alumni totals 637, and an additional 75 interns and residents are presently in training.

VIRGINIA

Welburn Award to Dr. Detwiler.—At the annual dinner of the Arlington County Medical Society, June 28, the third annual Welburn award for distinguished service to medicine in the community was bestowed on Dr. Robert H. Detwiler, Arlington, the first doctor to be so honored.

Symposium on Cardiology Postponed.—The Medical College of Virginia, Richmond, announces the postponement of the Symposium on Cardiology and Cardiac Surgery, originally scheduled for Dec. 12-14. The postponement is necessitated by the fact that Dr. Andre Cournand, New York City, the McGuire Lecturer, will be in Stockholm at that time to receive a Nobel prize. The date of the symposium will be announced later.

GENERAL

Meeting on Industrial Medicine.—The Central States Society of Industrial Medicine and Surgery will hold its fall meeting Dec. 2 at the Palmer House, Chicago, under the presidency of Dr. Leonard Arling, Minneapolis. The following program will be presented at 2 p. m.:

Ogilvie Paul, Chicago, The Employability of Cardiacs.
Karl H. Pfuetze, Chicago, Reemployment of the Extubercular Patient by Industry.
Joseph M. Dzish, Buffalo, Recent Advances in Surgery of Trauma.
Robert G. Thompson, Chicago, Amputations and the Newest Developments in Prostheses.
Mr. K. A. Carney, Chicago, Railroads' Approach to Medical Legal Problems.

Meeting on Air Pollution Control.—The semiannual meeting of the Air Pollution Control Association will be held at the Rice Hotel, Houston, Texas, Dec. 3-5. The morning session will feature a discussion of the Houston air pollution situation and its legal aspects in the Houston area. Other sessions will include symposiums on the odor problem, the sulfur problem, and the dust problem.

Course on Clinical Hypoxia.—The National Resuscitation Society Inc., formerly the Society for the Prevention of Asphyxial Death Inc., will present its 118th course in clinical hypoxia, featuring laryngoscopy and intubation, Dec. 7-8. Courses are

presented the first Friday afternoon and Saturday morning of each month at the New York Academy of Sciences, 2 E. 63rd St., New York City. Matriculation fee is $50. For information, address the Secretary, National Resuscitation Society Inc., 2 E. 63rd St., New York 21 (telephone, REgent 4-3515).

Surgical Essay Contest.—The Southeastern Surgical Congress announces its annual prize scientific paper award for 1957. The author of the best unpublished contribution on surgery or allied subjects will be awarded $100 and expenses to attend the next annual meeting of the congress in St. Petersburg, Fla. For information write Dr. Alva H. Letton, Chairman, Scientific Paper Award Committee, 478 Peachtree St., Atlanta, Ga.

Meetings on Nervous and Mental Disease.—The Association for Research in Nervous and Mental Disease will hold its 36th annual meeting at the Hotel Roosevelt, New York City, Dec. 7-8, under the presidency of Dr. Harry C. Solomon, Boston, to consider "The Brain and Human Behavior." The Friday afternoon session, which will be devoted to consideration of temporal and deep sylvian areas of the human brain, will be opened by Dr. Wilder G. Penfield, Montreal, Canada, who will discuss "Functional Localization in Temporal and Deep Sylvian Areas," and will close with "The Physiological and Anatomical Basis for the Functional Subdivisions of the Temporal Region" by Drs. Herbert H. Jasper and Theodore B. Rasmussen, Montreal. The Saturday program on pharmacology and behavior will include "Behavioral Changes After Intraventricular Injection of Drugs" by Dr. William S. Feldberg, London, England; "Physiology of the Corpus Callosum" by Dr. Frederic Bremer, Brussels, Belgium; and "Functional Plasticity in Cortical Speech Areas and the Integration of Speech" by Dr. H. Lamar Roberts, Montreal, Canada. In conjunction with the association meetings, the American League Against Epilepsy will hold its annual meeting Dec. 6 at the Hotel Roosevelt and the annual meeting of the Eastern Association of Electroencephalographers will convene Dec. 5 at the College of Physicians and Surgeons, Amphitheater A, Columbia-Presbyterian Medical Center.

Dermatologists Meet in Chicago.—The 15th annual meeting of the American Academy of Dermatology and Syphilology will convene at the Palmer House, Chicago, Dec. 8-13, under the presidency of Dr. George M. Lewis, New York City. The Paul A. O'Leary Memorial Lecture, "The Seborrheic Diathesis," will be given Monday morning by Dr. John T. Ingram, Leeds, England. On Tuesday at 8:30 p. m., Dr. Leonard L. Lovshin, Cleveland, will present the John E. Rauschkolb Memorial Lecture, "Signs That Aid in the Diagnosis of Functional Disease." Other special lectures include "The Importance of Mycologic Diagnostic Facilities in Medicine" by Norman F. Conant, Ph.D., Durham, N. C. (Sunday, 3:30 p. m.), and on Monday morning, "Structure and Function of Sebaceous Glands" by Dr. Walter C. Lobitz Jr., Hanover, N. H. and "Therapy of Seborrhea and Seborrheic Dermatitis" by Dr. Nelson P. Anderson, Los Angeles. An all-day symposium on pharmaceutical therapeutics has been scheduled for Thursday. In all, 14 other symposiums will be offered. On Tuesday afternoon there will be a panel on the diagnosis and treatment of cutaneous malignancy. Ten round-table panels will be given. An all-day clinicopathological conference has been arranged for Wednesday. Informal discussion groups are planned for Monday and Tuesday noon and afternoon and for Wednesday noon. Cocktails at 6:30 p. m. Wednesday will precede the banquet and entertainment at 7:30 p. m. (formal dress optional).

CANADA

International Congress in Toronto on Rheumatic Diseases.—The ninth International Congress on Rheumatic Diseases, a quadrennial function of La Ligue Internationale contre le Rhumatisme, will be held at Toronto, Canada, June 23-28, 1957, under the auspices of the Canadian Rheumatism Association. The program committee is anxious to receive reports on current clinical or basic research dealing with any aspect of the rheumatic diseases. A 200-word abstract of papers offered for consideration should be submitted not later than Jan. 1, 1957, in triplicate in the language in which the paper is to be read. If an abstract is submitted in a language other than English, an accompanying English translation will be helpful, though not essential. All correspondence should be directed to: The Ninth International Congress on Rheumatic Diseases, Post Office Box 237, Terminal "A," Toronto, Ontario, Canada.

CORRECTIONS

Treatment of Subacute Bacterial Endocarditis.—In the Query and Minor Note on subacute bacterial endocarditis in THE JOURNAL, Sept. 22, 1956, page 435, line 18 of the first paragraph, which reads "4 million units of crystalline benzathine penicillin G," should have read "4 million units of crystalline benzyl penicillin G."

Lead Poisoning.—In the initial summary of the article by Dr. Harold Jacobziner in THE JOURNAL, Sept. 29, 1956, page 454, right-hand column, lines 10 and 11, the statement should read "and children in the 1-3 year age group accounted for 70 out of 80 cases of lead poisoning observed in children under the age of 7 years."

EXAMINATIONS AND LICENSURE

AMERICAN BOARD OF ANESTHESIOLOGY: *Part I.* Various locations, July 19. Final date for filing application is Jan. 19. *Oral.* Asheville, No. Car., Mar. 24-29. Sec., Dr. Curtiss B. Hickcox, 80 Seymour St., Hartford 15, Conn.

AMERICAN BOARD OF INTERNAL MEDICINE: *Subspecialties. Gastroenterology.* Philadelphia, April 5-6. Final date for filing application is March 1. Exec. Sec., Dr. W. A. Werrell, 1 West Main St., Madison 3, Wis.

AMERICAN BOARD OF NEUROLOGICAL SURGERY: Examination given twice annually, in the spring and fall. In order to be eligible a candidate must have his application filed at least six months before the examination time. Sec., Dr. Leonard T. Furlow, Washington University School of Medicine, St. Louis 10.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY: *Part I.* Various cities of the United States, Canada, and military centers outside the Continental United States, Feb. 1. Candidates must submit case reports to the office of the Secretary within thirty days of being notified of their eligibility to Part I. The cases must be prepared in the manner described in the Bulletin of the board with a duplicate index list. *Part II.* Chicago, May 16-25. Request for reexamination in Part II must be received prior to Feb. 1. Sec., Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland 6, Ohio.

AMERICAN BOARD OF OPHTHALMOLOGY: *Written.* Jan. 21. Final date for filing application was July 1. *Oral.* New York, May 23-27; Chicago, Oct. 7-11. Sec., Dr. Merrill J. King, Box 258, Cape Cottage Branch, Portland 9, Maine.

AMERICAN BOARD OF ORTHOPAEDIC SURGERY: *Oral. Part II.* Chicago, January 1957. Final date for filing application was Aug. 15. Sec., Dr. Sam W. Banks, 110 South Michigan Ave., Chicago 3.

AMERICAN BOARD OF OTOLARYNGOLOGY: Chicago, Oct. 7-11. Final date for filing application is April. Sec., Dr. Dean M. Lierle, University Hospitals, Iowa City.

AMERICAN BOARD OF PATHOLOGY: *Oral and Written. Pathologic Anatomy and Clinical Pathology.* Washington, April 4-6. Final date for filing application is March 1. Sec., Dr. Edward B. Smith, 1040 West Michigan St., Indianapolis 5.

AMERICAN BOARD OF PEDIATRICS: *Oral. Part II.* San Francisco, Dec. 7-9. Sec., Dr. John McK. Mitchell, 6 Cushman Road, Rosemont, Pa.

AMERICAN BOARD OF PHYSICAL MEDICINE AND REHABILITATION: *Parts I and II.* New York City, June 8-9. Final date for filing application is March 1. Sec., Dr. Earl C. Elkins, 200 First St., S.W., Rochester, Minn.

AMERICAN BOARD OF PLASTIC SURGERY: *Entire Examination.* Philadelphia, May 4-6. Final date for filing case reports is Jan. 1. Corres. Sec., Mrs. Estelle E. Hillerich, 4647 Pershing Ave., St. Louis 8.

AMERICAN BOARD OF PREVENTIVE MEDICINE: *Oral and Written. Public Health.* Philadelphia, Nov. 8-10. Sec., Dr. Ernest L. Stebbins, 615 N. Wolfe St., Baltimore, Md.

AMERICAN BOARD OF PLASTIC SURGERY: *Parts I and II.* Philadelphia, September. Final date for filing application is March 1. Sec., Dr. Stuart T. Ross, 520 Franklin Ave., Garden City, New York.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: *Oral.* New York, Dec. 10-11 and New Orleans, Mar. 18-19. Final date for filing application was Sept. 10. Sec., Dr. David A. Boyd, Jr., 102-110 Second Ave., S.W., Rochester, Minn.

AMERICAN BOARD OF RADIOLOGY: Tampa, April 1-6. Final date for filing application is Jan. 1. Washington, Sept. 23-28. Final date for filing application is June 1. Sec., Dr. B. R. Kirklin, Kahler Hotel Bldg., Rochester, Minn.

AMERICAN BOARD OF SURGERY: *Part II.* Kansas City, Kan., Dec. 10-11; Los Angeles, Jan. 14-15; San Francisco, Jan. 17-19; Houston, Feb. 18-19; Nashville, Mar. 11-12; Boston, April 8-9, and New York, June 10-11.

AMERICAN BOARD OF UROLOGY: February 1957. Sec., Dr. William Niles Wishard, 1711 N. Capital Ave., Indianapolis 7.

BOARD OF THORACIC SURGERY: *Written.* Various centers throughout the country, February 1957, and the closing date for registration is Dec. 1, 1956. Sec., Dr. William M. Tuttle, 1131 Taylor Ave., Detroit 2.

DEATHS

Plass, Everett Dudley ● Saranac Lake, N. Y.; born in Poughkeepsie May 6, 1886; Johns Hopkins University School of Medicine, Baltimore, 1911; formerly on the faculty of his alma mater; professor emeritus of obstetrics and gynecology at the State University of Iowa College of Medicine, Iowa City, where for many years he was professor and head of the department; member, past-president, and secretary of the Central Association of Obstetricians and Gynecologists; member of the Iowa State Medical Society and the American Gynecological Society; secretary, Section on Obstetrics, Gynecology and Abdominal Surgery of the American Medical Association from 1934 to 1937, when he became chairman of the Section on Obstetrics and Gynecology, serving until 1938; specialist certified by the American Board of Obstetrics and Gynecology and formerly a member; served as a member of the National Board of Medical Examiners; veteran of World War I; obstetrician-in-chief at the Henry Ford Hospital in Detroit from 1922 to 1926; died Aug. 17, aged 70, of ruptured aortic aneurysm.

Scott, James Robert ● Santa Fe, N. Mex.; born in Hamden, N. Y., April 29, 1886; Cooper Medical College, San Francisco, 1912; served as the anatomist and microscopist for the Army Medical Museum in Washington, D. C., and pathologist for the Los Angeles County Hospital in Los Angeles and the Baker Clinic in Baker City, Ore.; served as an associate professor of pathology and bacteriology at the University of South Dakota in Vermillion, and as the associate professor of health education at the University of New Mexico in Albuquerque; from 1928 to 1933 county health officer in Albuquerque; later district health officer; in 1940 became director of the New Mexico Department of Public Health, which position he held until 1953, when he became district health officer for Dona Ana County, fourth district, Las Cruces; retired Aug. 1, 1956, returning to Santa Fe; member of the governing council of the American Public Health Association and its official delegate; past-president of the New Mexico Public Health Association; died in St. Vincent Hospital Sept. 14, aged 70, of diabetes mellitus and pneumonia.

Love, Ben Del, Jr., Nashville, Tenn.; born in Pauls Valley, Okla., March 4, 1918; Meharry Medical College, Nashville, 1950; interned at the George W. Hubbard Hospital of Meharry Medical College, where he served a residency; from 1952 to 1954 a research fellow in medicine at the Thorndike Memorial Laboratory of the Boston City Hospital in Boston, and a research fellow in medicine at Harvard Medical School in Boston; assistant professor of microbiology, and instructor of medicine at his alma mater, where he was director of the Holman Memorial Laboratory and chairman of the committee on hospital laboratories; on the staff of the George W. Hubbard Hospital of Meharry Medical College, where he died Sept. 2, aged 38, of subarachnoid hemorrhage.

Safford, Henry Barnard ● New York City; born in 1883; New York Homeopathic Medical College and Flower Hospital, New York City, 1908; emeritus professor of obstetrics and gynecology at the New York Medical College, Flower and Fifth Avenue Hospitals; specialist certified by the American Board of Obstetrics and Gynecology; fellow of the American College of Surgeons; consultant at the Mother Cabrini Memorial and Metropolitan hospitals; a long-time chief of staff for gynecology and obstetrics at Flower and Fifth Avenue Hospitals; author of "That Bennington Mob," "The Intimate Problems of Women," and "Tell Me, Doctor"; had conducted a monthly column under the latter title in the *Ladies Home Journal* since 1951; died in the Nassau Hospital, Mineola, Sept. 16, aged 72, of coronary occlusion.

Nassauer, Charles Halpin, New York City; born in New York City March 31, 1888; Columbia University College of Physicians and Surgeons, New York City, 1912; for many years police department surgeon; professor of medicine, New York Polyclinic Medical School and Hospital; formerly on the faculty of the New York University College of Medicine and the New York University Post-Graduate Medical School; specialist certified by the American Board of Internal Medicine; member of the Medical Society of the State of New York; on the staffs of the Bellevue and University hospitals; consultant at Misericordia Hospital and the New York Infirmary; died Sept. 29, aged 68, of coronary disease.

Layne, Charles Wesley ● Newburgh, N. Y.; born in Pembroke, Ky., Nov. 16, 1900; Emory University School of Medicine, Atlanta, Ga., 1928; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; member of the American Heart Hospital and the American Diabetes Association; for many years on the staff of Craig House in Beacon, where he was a consultant; on the consulting staff of the Harlem Valley State Hospital in Wingdale, the Matteawan State Hospital in Beacon, and St. Anthony's Hospital in Warwick; on the staff of St. Luke's Hospital; died Sept. 21, aged 55.

Acker, Charles Thomas ● Montevallo, Ala.; Birmingham Medical College, Birmingham, 1900; died Oct. 1, aged 78.

Barnes, George McMaster ● Belzoni, Miss.; Memphis Hospital Medical College, Memphis, Tenn., 1908; past-president of the Delta Medical Society; on the staff of the Humphreys County Memorial Hospital, where he died Sept. 14, aged 71, of acute coronary occlusion.

Bartlett, Grove Willis, Belgrade, Neb.; Omaha Medical College, Omaha, 1900; died Sept. 8, aged 78, of heart disease.

Beattie, Robert ● Detroit; Detroit College of Medicine, Detroit, 1903; served on the faculty of his alma mater, now known as the Wayne University College of Medicine; member of the American Academy of Ophthalmology and Otolaryngology; fellow of the American College of Surgeons; veteran of World War I; on the staff of the Providence Hospital; died in Clare Aug. 18, aged 85, of arteriosclerosis.

Bengelsdorf, Aron Albert ● Newark, N. J.; Albertus-Universität Medizinische Fakultät, Königsberg, Prussia, Germany, 1914; an officer in the Russian Army during World War I; on the staffs of Newark Beth Israel, Presbyterian, and St. Michael's hospitals; died Sept. 13, aged 65, of a heart attack.

Knapp, Edward Volney, San Anselmo, Calif.; Cooper Medical College, San Francisco, 1907; an associate member of the American Medical Association; formerly on the staff of the St. Luke's Hospital in San Francisco; died Sept. 28, aged 78, of coronary thrombosis.

Kuhn, Orta Edward, South Pasadena, Calif; Stanford University School of Medicine, San Francisco, 1917; an associate member of the American Medical Association; died in the Collis P. and Howard Huntington Memorial Hospital, Pasadena, Sept. 3, aged 73, of myocardial infarction.

La Rocca, Joseph ● Valparaiso, Ind.; University of Illinois College of Medicine, Chicago, 1920; died in the Porter Memorial Hospital Sept. 25, aged 59, of heart disease.

Lingeman, Leslie Roberts, Maryville, Tenn.; Indiana University School of Medicine, Indianapolis, 1917; specialist certified by the American Board of Radiology; member of the Radiological Society of North America; served on the staff of the Blount Memorial Hospital; died Aug. 8, aged 64.

Livengood, Baxter Alphonso ● Woodbury, N. J.; University of Pennsylvania School of Medicine, Philadelphia, 1925; member of the American Academy of General Practice; served as an officer in the U. S. Navy; past-president of the Gloucester County Medical Society; on the staff of the Memorial Hospital; died Sept. 7, aged 57.

Long, Oscar B., Philomath, Ore.; Tennessee Medical College, Knoxville, Tenn., 1907; died Aug. 26, aged 80, of cardiovascular renal disease.

Margulis, Sidney Herbert ● Buffalo; University of Buffalo School of Medicine, Buffalo, 1938; specialist certified by the American Board of Internal Medicine; veteran of World War II; associate in medicine at his alma mater; on the staffs of the Edward J. Meyer Memorial Hospital, Veterans Administration Hospital, and the Millard Fillmore Hospital, where he died Sept. 19, aged 44, of acute myocardial infarction and coronary occlusion.

● Indicates Member of the American Medical Association.

Mathae, George Herman ● St. Louis; St. Louis University School of Medicine, St. Louis, 1909; also a dentist and lawyer; on the staff of the Bethesda General Hospital and the Lutheran Hospital, where he died Sept. 22, aged 74, of cerebral arteriosclerosis.

McGee, James Patton ● Oklahoma City; Emory University School of Medicine, Atlanta, Ga., 1916; professor of ophthalmology at the University of Oklahoma School of Medicine; died in St. Anthony Hospital Sept. 11, aged 65, of myocardial infarction.

McHugh, Francis Thomas ● Chippewa Falls, Wis.; Bennett Medical College, Chicago, 1911; interned at the Cook County Hospital in Chicago; died Sept. 5, aged 75, of coronary thrombosis.

McLeod, Frederick Leon, Los Angeles; Lincoln Medical College of Cotner University, Lincoln, Neb., 1901; College of Physicians and Surgeons, Baltimore, 1907; an associate member of the American Medical Association; formerly practiced in Lincoln, Neb., where he was on the staff of St. Elizabeth Hospital; died Aug. 24, aged 77, of subarachnoid hemorrhage and congestive heart disease.

Meredith, Loren Kenneth ● Des Moines, Iowa; University of Michigan Medical School, Ann Arbor, 1916; member of the American Academy of General Practice and the Association of Life Insurance Medical Directors of America; veteran of World War I; medical director for the National Life Company and the Iowa Life Insurance Company; died in the Rochester Methodist Hospital, Rochester, Minn., Sept. 13, aged 65, of an abdominal hemorrhage.

Miller, George William ● Norristown, Pa.; Jefferson Medical College of Philadelphia, 1906; fellow of the American College of Surgeons; served as professor of general anatomy in the Temple University School of Dentistry, Philadelphia, as associate in anatomy at his alma mater, and on the staff of the department of applied anatomy at Temple University School of Medicine in Philadelphia; veteran of World War I; on the staffs of the Sacred Heart Hospital and the Montgomery Hospital, where he died Sept. 5, aged 74, of chronic lymphatic leukemia.

Moore, Leland Oliver Walter ● Colonel, U. S. Army, retired, Washington, D. C.; Cooper Medical College, San Francisco, 1912; veteran of World War I; entered the Medical Corps of the U. S. Army in 1920 and retired Nov. 30, 1945; fellow of the American College of Surgeons; formerly professor of military science and tactics at George Washington University School of Medicine; died in the Walter Reed Army Hospital Aug. 28, aged 67, of cancer.

Murphy, Jewyl Booth, Redwood City, Calif.; University of Texas School of Medicine, Galveston, 1922; member of the American Academy of Pediatrics; interned at the Children's Hospital in San Francisco, where she was on the staff of the University of California Hospital; formerly on the staff of the Community Hospital of San Mateo County in San Mateo; died Aug. 30, aged 60, of carcinoma of the colon.

Nelson, Oscar Emil, Stewart, Minn.; Chicago College of Medicine and Surgery, Chicago, 1910; died Aug. 19, aged 79, of cancer.

Nicoll, Alexander, New York City; Columbia University College of Physicians and Surgeons, New York City, 1903; an associate member of the American Medical Association; fellow of the American College of Surgeons; veteran of World War I; at one time on the faculty of Fordham University School of Medicine; served on the staffs of the Central Suffolk Hospital in Riverhead, St. Elizabeth's, Fordham, Mother Cabrini Memorial and St. Francis' hospitals; died in the Southside Hospital, Bay Shore, Sept. 24, aged 75.

Nilson, Helmer Jonas ● North Mankato, Minn.; University of Minnesota Medical School, Minneapolis, 1932; member of the American Academy of General Practice; served as health officer; on the staffs of St. Joseph's Hospital and the Immanuel Hospital, Mankato, where he died Aug. 31, aged 63, of a coronary attack.

North, William R. ● Nokomis, Fla.; Beaumont Hospital Medical College, St. Louis, 1900; member of the Missouri State Medical Association; formerly practiced in St. Louis, where he was on the staff of the Evangelical Deaconess Hospital; died in Labadie, Mo., Aug. 29, aged 80, of cancer.

Ogden, Arthur White ● Joliet, Ill.; the Hahnemann Medical College and Hospital, Chicago, 1913; died Aug. 17, aged 72, of arteriosclerotic heart disease.

Ogden, Michael Alexander ● Passaic, N. J.; University of Odessa Faculty of Medicine, Odessa, Russia, 1918; specialist certified by the American Board of Pathology; fellow of the American College of Physicians; served on the faculty of the Louisiana State University School of Medicine in New Orleans; for many years on the staff of the Passaic General Hospital, where he died Sept. 13, aged 63, of coronary disease.

Oliver, Adlai Stevenson ● Raleigh, N. C.; Jefferson Medical College of Philadelphia, 1914; specialist certified by the American Board of Obstetrics and Gynecology; on the staffs of the Rex and St. Agnes hospitals; died Aug. 20, aged 64, of coronary artery disease.

Orr, James Edward, Seneca, S. C.; Medical College of South Carolina, Charleston, 1931; died Aug. 28, aged 53, of coronary thrombosis.

Outland, James Alfred, Murray, Ky.; University of Louisville School of Medicine, Louisville, 1912; member of the Kentucky State Medical Association; public health physician for Graves, Calloway, and Trigg counties; died Aug. 24, aged 71, of cancer.

Mackenzie, Simon Samuel ● Akron, Ohio; University of Buffalo School of Medicine, Buffalo, 1897; for many years practiced in Warren, where he was on the staff of the Warren Memorial Hospital; died Aug. 24, aged 83, of heart disease.

Pace, Arthur Albert ● Toledo, Iowa; Detroit College of Medicine, Detroit, 1896; veteran of World War I; served as mayor, councilman, and member of the school board; formerly associated with the Indian Service; on the staff of the Evangelical Hospital, Marshalltown; died Aug. 8, aged 86, of heart disease.

Palmer, Mary Simpson McCarty, Orchard Lake, Mich.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1886; died Sept. 11, aged 94, of heart disease.

Pedrick, William Weaver ● Glassboro, N. J.; Temple University School of Medicine, Philadelphia, 1922; member of the Industrial Medical Association; for many years president of the Gloucester County Health Association, and physician for the public schools; past-president of the board of health; died in the Elmer (N. J.) Community Hospital Aug. 10, aged 60, of coronary thrombosis.

Philo, Rae Morris, New Haven, N. Y.; Syracuse University College of Medicine, Syracuse, 1913; died July 28, aged 67, of angina pectoris.

Price, John Thomas, Harrodsburg, Ky.; Hospital College of Medicine, Louisville, 1895; an associate member of the American Medical Association; died in the James B. Haggin Memorial Hospital Aug. 14, aged 88.

Price, Lucius Grant, St. Petersburg, Fla.; University of Pennsylvania Department of Medicine, Philadelphia, 1890; died Aug. 12, aged 89, of arteriosclerosis.

Quinn, Francis Peter ● Dubuque, Iowa; State University of Iowa College of Medicine, Iowa City, 1921; member of the American Academy of Ophthalmology and Otolaryngology; served during World War II; died Aug. 8, aged 64, of bronchial asthma.

Rauchschwalbe, Lothar Ernst ● Oconto Falls, Wis.; Loyola University School of Medicine, Chicago, 1930; on the staff of the Community Memorial Hospital; died Aug. 12, aged 53, of coronary occlusion.

Rebbeck, Elmer William, Pittsburgh; Hahnemann Medical College and Hospital of Philadelphia, 1925; an associate member of the American Medical Association, fellow of the American College of Surgeons; veteran of World War II; on the staff of the Shadyside Hospital, where he died Aug. 19, aged 54, of arteriosclerotic heart disease and pulmonary embolism.

Rice, Edward Martin ● Wauwatosa, Wis.; Milwaukee Medical College, Milwaukee, 1903; also a graduate in law; honorary member of the staff, St. Luke's Hospital in Milwaukee; died Aug. 26, aged 83, of uremia.

Roberts, Edward Russell ● Bridgeport, Conn.; Medical School of Maine, Portland, 1913; specialist certified by the American Board of Otolaryngology; member of the American Laryngological, Rhinological and Otological Society; fellow of the American College of Surgeons; veteran of World War I; past-president of the Bridgeport Medical Society; on the staff of the Bridgeport Hospital; died Aug. 26, aged 67, of cerebral hemorrhage.

Robertson, William S., Danville, Va.; College of Physicians and Surgeons, Baltimore, 1885; died in Lynchburg Aug. 23, aged 93, of cerebral vascular accident and arteriosclerosis.

Rogers, Edmund Augustus ● Brookline, Mass.; Baltimore Medical College, Baltimore, 1904; veteran of World War I; died in the New England Deaconess Hospital, Boston, Aug. 31, aged 74, of acute myocardial infarction.

Schwarzmann, Markus ● New York City; Julius-Maximilians-Universität Medizinische Fakultät, Würzburg, Bavaria, Germany, 1922; died Sept. 6, aged 63, of cancer of the rectum.

Spearman, Clyde Herman, Coffeeville, Miss.; University of Nashville Medical Department, Nashville, Tenn., 1906; died Sept. 17, aged 72, in an automobile accident.

Spencer, Floyd Henry ● St. Joseph, Mo.; Central Medical College of St. Joseph, 1900; veteran of World War I; past-president of the Buchanan County Medical Society; past-president of the city board of health; member and past-president of the staff, Missouri Methodist Hospital; member of the staff of St. Joseph's Hospital; past-president of the staff of State Hospital No. 2; died in the Veterans Administration Hospital, Wadsworth, Kan., Oct. 4, aged 77, of cardiac hypertrophy.

Stapp, Fred Brown ● Chattanooga, Tenn.; Bellevue Hospital Medical College, New York City, 1884; past-president of the Hamilton County Medical Society; for many years medical examiner for Metropolitan Life Insurance Company; served as chief of staff at Baroness Erlanger Hospital; died Aug. 4, aged 95.

Stattman, Bernard ● Brooklyn, N. Y.; University and Bellevue Hospital Medical College, New York City, 1908; on the staff of the Samaritan Hospital, where he died Aug. 27, aged 69, of coronary thrombosis.

Steele, Ernest Richmond, Dover, Del.; Jefferson Medical College of Philadelphia, 1901; died in the Kent General Hospital June 29, aged 80, of myocardial infarction.

Stewart, Thomas Weir ● Lithonia, Ga.; University of Louisville Medical Department, Louisville, Ky., 1915; died Aug. 13, aged 69, of pulmonary edema and coronary occlusion.

Swanson, Albert John, Costa Mesa, Calif.; Chicago College of Medicine and Surgery, Chicago, 1908; an associate member of the American Medical Association; died July 10, aged 74, of cancer.

Swetlow, George Irving ● Brooklyn, N. Y.; Long Island College Hospital, Brooklyn, N. Y., 1920; also a lawyer; served on the faculty of the Brooklyn Law School; fellow of the American College of Physicians; consulting neuropsychiatrist at Cumberland Hospital; died in the Brooklyn Hospital Aug. 20, aged 58, of pulmonary edema, coronary heart disease, and diabetes mellitus.

Taylor, Willis Harvey, Omaha; University of Nebraska College of Medicine, Omaha, 1911; professor emeritus of clinical obstetrics and gynecology at his alma mater; an associate member of the American Medical Association; member of the Central Association of Obstetricians and Gynecologists; fellow of the American College of Surgeons; in 1941 elected president of the Nebraska Methodist Hospital; on the staff of the Immanuel Hospital; died Aug. 3, aged 69, of coronary thrombosis.

Thomson, Joseph Oscar, Stillwater, Okla.; McGill University Faculty of Medicine, Montreal, Canada, 1909; for many years a missionary in China; fellow of the American College of Surgeons; formerly physician at the Oberlin College in Oberlin, Ohio; served as medical director for the General Motors Tank Plant in Flint, Mich.; retired in 1951 from the faculty of the Oklahoma Agricultural and Mechanical College; died in the Stillwater Municipal Hospital Oct. 2, aged 71, of cerebral hemorrhage.

Tompkins, Rutledge Chaney, Minden, La.; University of Nashville Medical Department, Nashville, Tenn., 1901; for many years coroner of Webster Parish, and associated with the Webster Parish Health Unit in Minden and Springhill; at one time medical superintendent of the State Colony and Training School in Alexandria; died July 21, aged 79, of coronary thrombosis.

Totman, Harold Maydole ● Syracuse, N. Y.; Syracuse University College of Medicine, Syracuse, 1924; veteran of World War I; served on the staff of St. Joseph's Hospital; medical director of the Unity Life and Accident Insurance Company; died in St. Joseph's Hospital Aug. 5, aged 59, of lung cancer.

Townsend, Jesse P., Berryman, Mo.; Beaumont Hospital Medical College, St. Louis, 1897; died in the Farmington (Mo.) State Hospital Sept. 2, aged 83.

Trippel, Edward ● O'Fallon, Ill.; St. Louis University School of Medicine, St. Louis, 1912; died in St. Elizabeth's Hospital, Belleville, Aug. 22, aged 67, of diabetes mellitus.

Voorhees, Bert Grant, Elmira, N. Y.; Jefferson Medical College of Philadelphia, 1914; an associate member of the American Medical Association; served in France during World War I; on the staffs of Arnot-Ogden Memorial and St. Joseph's hospitals; died Sept. 29, aged 70, of cerebral hemorrhage.

Waddell, William Everett, Los Angeles; Pulte Medical College, Homeopathic, Cincinnati, 1887; specialist certified by the American Board of Otolaryngology; an associate member of the American Medical Association; fellow of the American College of Surgeons; served on the staff of St. Vincent's Hospital, where he died Aug. 24, aged 91, of pulmonary thrombosis.

Walch, John Joseph ● Escanaba, Mich.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1912; past-president of the Upper Peninsula Medical Society; served as a member of the state board of registration in medicine; past-president of the Delta County Medical Society; formerly a member of the board of education; a member of the board of directors of the State Bank of Escanaba; on the staff of St. Francis Hospital, where he died Sept. 5, aged 69, of cerebral thrombosis.

Weisbrod, Samuel Lyon, Milford, Mich.; Trinity Medical College, Toronto, Ontario, Canada, 1894; died Aug. 21, aged 87, of coronary thrombosis.

Wheelock, Harry Elmer ● Fredonia, N. Y.; Jefferson Medical College of Philadelphia, 1914; fellow of the American College of Surgeons; veteran of World War I; for many years a member and president of the school board; a member of the board of visitors of Fredonia State Teachers College, and of the Roswell Park Memorial Institute in Buffalo; on the staff of the Brooks Memorial Hospital in Dunkirk, where he died Aug. 25, aged 65, of coronary thrombosis.

Whitehead, John Maloy ● Indianapolis; Indiana University School of Medicine, Indianapolis, 1918; veteran of World War I; retired chief anesthetist for Methodist Hospital, where he died Aug. 9, aged 67, of cerebral infarction.

Wiese, Milton Arthur ● Libertyville, Ill.; University of Illinois College of Medicine, Chicago, 1914; on the staffs of St. Therese Hospital in Waukegan and the Condell Memorial Hospital in Libertyville, where he died Sept. 18, aged 64, of coronary occlusion.

Willey, Arthur J., Marion, Ohio; Ohio Medical University, Columbus, 1898; fellow of the American College of Surgeons; also a dentist; on the staff of the Marion General Hospital; died Sept. 1, aged 84, of cerebral hemorrhage.

Williams, Frederick Russell ● Worcester, Mass.; Long Island College Hospital, Brooklyn, N. Y., 1905; died in the Memorial Hospital Aug. 10, aged 73.

Williamson, Walter Scott ● Captain, U. S. Army, San Antonio, Texas; University of Oklahoma School of Medicine, Oklahoma City, 1950; interned at the Mercy Hospital and at the University Hospitals in Oklahoma City, Okla.; resident at the Brooke Army Hospital; died in Fort Sam Houston July 8, aged 34, of coronary thrombosis.

Winters, William Winfred, Boliver, Tenn.; University of Nashville Medical Department, 1904; veteran of World War I; formerly on the staff of the Western State Hospital in Western State Hospital; at one time on the staff of the Veterans Administration Hospital in Minneapolis; served as resident physician at the Davidson County Hospital in Nashville; died Aug. 14, aged 80, of bronchopneumonia and adenocarcinoma of the prostate.

Williams, Philip Banatyne, Rome, Pa.; Jefferson Medical College of Philadelphia, 1895; died in the Robert Packer Hospital, Sayre, Aug. 11, aged 82, of arteriosclerotic heart disease.

FOREIGN LETTERS

AUSTRIA

Tuberculous Appendicitis.—At the meeting of the Society for Pediatrics in Vienna on May 9, Dr. H. H. Orel presented the case of a 14-year-old boy who had received orthopedic treatment since his 4th year because of the sequels of tuberculous coxitis. In February, 1956, a tuberculous inflammation of the knee joint had developed after a fall. In the middle of March, the patient had an acute attack of appendicitis and his appendix was removed. Several days after the operation, symptoms of a tuberculous meningitis appeared, and clinical and bacteriological studies corroborated this diagnosis. The meningitis subsided after treatment with streptomycin. Histological examination of the removed appendix revealed tuberculosis of the appendix. The concurrence of the tuberculous appendicitis, meningitis, and arthritis is regarded as the result of a hematogenous dissemination of the tuberculosis resulting from the fall. Dr. Orel stated that the appendicitis was an isolated process.

Personality of Obese Children.—At the same meeting Dr. H. E. Huber reported personality studies of 50 obese children and 50 children of normal weight. The obese children came from families that were not unusual except that there seemed to be a familial tendency to obesity; most of the children ate more than the average child, and their play and games usually involved little exercise. Intelligence tests revealed that the obese children had normal intelligence, memory, perseverance, dexterity, and fantasy and average school performances, but they were relatively inactive, slow or lazy, and defective in social contacts. This last factor was not primary but was the result of the reactions of others to their physical abnormality and their inactivity.

SWITZERLAND

Aldosterone Hypersecretion in Pituitary Basophilism and Adrenal Cortical Hyperfunction.—For many years it was supposed that a hypersecretion of mineralocorticoids might play a role in the pathogenesis of those cases of pituitary basophilism and adrenal cortical hyperfunction that were associated with edema, polyuria, hypernatremia, alkalosis, and hypokalemia, but no conclusion could be reached until a method of assaying the urinary excretion of aldosterone became available. J. P. Doret (*Semaine hôp. Paris* 32:2921, 1956) found the mineralocorticoid level to be either normal or increased in patients with this condition but could not explain these contradictory findings. In the three patients with this condition reported, the presence of a marked retention of water and sodium and of alkalosis with hypokalemia suggested hyperaldosteronism. In the first case, which occurred subsequent to a large chromophobe tumor, no hormone evaluation was available; in the second (reported by Brown and co-workers), there was an increase in excretion of aldosterone; and in the third (the author's second case), due to the presence of a mixed adenocarcinoma of the pituitary gland, hyperaldosteronuria could be demonstrated.

Streptococcus Typing.—A. Rivkine (*Schweiz. med. Wchnschr.* 86:1098, 1956) reports an attempt to type the hemolytic streptococci in children of a more or less homogeneous environment (from orphanages and boarding schools). He found that, since virulence is a potential and labile characteristic, independent of the strain of the pathogen, it is not possible to predict whether a carrier will be dangerous. No laboratory test reveals the virulence for man of a given strain. A strain from a sick carrier is more likely to be virulent than one from a healthy carrier. The occurrence of a disease in the carrier of a virulent strain depends on the susceptibility or resistance of the carrier. The communicability of a strain does not seem to be correlated with its virulence. If patients are to be isolated, those with the same type should be grouped together. Even when this precaution is taken, there is the risk of reimplantation of the common strain at an increased level of virulence.

UNITED KINGDOM

Hepatic Coma.—Dr. Sheila Sherlock and co-workers (*Lancet* 2:689, 1956) showed that clinical findings similar to those in spontaneously developing hepatic coma can be induced in patients with liver disease by the oral administration either of a high-protein diet or of nitrogenous compounds, such as urea or methionine. They believe that, by passing through a diseased liver, nitrogenous materials in the intestine reach the systemic circulation and thus the brain. This theory suggested the treatment of impending hepatic coma by withdrawal of protein and nitrogen-containing substances. The authors reported a series of 66 patients with liver disease complicated by hepatic coma or precoma whom they treated in this way. As the bacterial flora of the small intestine are increased in hepatic cirrhosis, chlortetracycline was administered to reduce their number and their effect on methionine. The patients suffered from such conditions as acute viral hepatitis, hepatic cirrhosis, obstructive jaundice, and ischemic necrosis of the liver. Three lines of treatment were used: 1. The intestines were emptied and kept free of all nitrogen-containing substances. 2. All dietary protein was stopped. 3. About 1,600 calories were supplied daily as glucose drinks or as 20% glucose given through an intragastric drip or, if necessary, as dextrose given intravenously. During the recovery period, protein was added in 20-gm. increments on alternate days. Any relapse was treated by withdrawing all protein. The lower intestine was emptied by an enema, and an oral dose of magnesium sulfate was given each day. The dose of chlortetracycline was 2 gm. initially, followed by 0.5 gm. every six hours for the duration of the symptoms or to a maximum of one week. As patients in impending hepatic coma are sensitive to sedatives, these were avoided whenever possible. Drugs known to induce hepatic coma, such as ammonium salts, acetazolamide, and morphine, were not used. A common precipitant of hepatic coma is gastroesophageal hemorrhage, which increases the nitrogen content of the intestine. This was treated with a Sengstaken esophageal compression balloon. Of the 66 patients, 39 recovered; of these, 21 had been in deep coma. Sodium glutamate was given intravenously to some patients but without effect. In view of the extremely poor prognosis of hepatic coma treated by other methods, the authors believe that the protein-withdrawal treatment represents an advance. Some patients received low-protein diets for two years and maintained body weight and positive nitrogen balance.

Effect of Giving Live Influenza Virus.—Immunization against epidemic influenza is normally done by subcutaneous inoculation of virus inactivated by formaldehyde. Chick embryos are used for growing the virus. However, as there would not be enough fertile eggs available to supply sufficient inactivated virus in the event of a severe influenza epidemic, Isaacs and Roden, of the medical research council and the common cold research unit have tried inoculating volunteers with live influenza-A virus prepared by one amniotic passage and either 1, 4, or 10 allantoic passages in chick embryos. The inoculum contained between 10^4 and 10^6 egg-infective doses. The initial inoculation was done intranasally, but subsequently it was done by pharyngeal spray. Seventeen volunteers participated in four separate trials. No symptoms of respiratory infection developed; no virus was recovered from the volunteers; and no increase in serum antibody to the influenza antigen was observed. It was therefore concluded that the virus lost its ability to multiply in man and that this method would be unsuitable for mass immunization.

The items in these letters are contributed by regular correspondents in the various foreign countries.

Health in Ceylon.—A health survey published by the Ministry of Health of Ceylon reveals the advances that have been made in medical treatment and public health in only a decade (D. M. Silva, Health Progress in Ceylon, Colombo, Ceylon). In seven years the general death rate has been halved; now it is 10.9 per 1,000, which is lower than that of Great Britain. Similarly, the infant mortality rate has been halved in the same period; it is now 71 per 1,000 live births. Maternal mortality has fallen to less than a third of the figure of seven years ago. These changes are not surprising in view of the large increase in expenditure for health services in Ceylon since dominion status was conferred on it in 1948. The expenditure per capita for health in 1945 was only three rupees; in 1953, it was 11 rupees. Health services have expanded, being partly aided by the World Health Organization and the Colombo Plan. One of the biggest contributions to public health has been the control of malaria, which until recently was responsible for more morbidity than any other disease. In 1946, there were 2,750,000 cases in Ceylon, or 412 per 1,000 population, with a death rate of 1.8 per 1,000. After 1947, all infected persons were treated and every habitation sprayed with chlorophenothane (DDT). In eight years the morbidity rate has been reduced from 412 to less than 5 per 1,000.

Tuberculosis is a severe endemic disease in Ceylon. Over 2 million of the population of 8 million have had a tuberculin skin test, and nearly a million negative reactors were given BCG vaccination. Mass miniature radiography, which was started in 1950, showed that 1% of all those examined had active tuberculosis. The death rate from this disease has been halved in the last three years, but ancylostomiasis still presents a problem and is responsible for more ill health than tuberculosis. A decade ago a third of the rural population was undernourished, not because of a shortage of food but because poverty prevented them from buying it. The lot is improving, but 10% of all school children still show signs of malnutrition. Cows are also undernourished, and this affects the quality and quantity of milk. The average yield per cow is only 60 gal., which is about a 10th that of a normal pasture-fed cow in Great Britain. The per capita consumption of milk in Ceylon is therefore only 2 oz. daily. The government issues free imported dried milk to about 250,000 people daily.

The improved health and nutrition services have resulted in a large increase in the population. The excess of births over deaths is now 28.5 per 1,000, compared with 4.5 in Great Britain; it is the highest figure in the world. This in itself presents a problem, because money must be found for more food, more schools, and more houses to keep pace with the rising population. This may make it difficult to find funds to maintain high standards of medical care, nutrition, and education. Large areas in the northeast of the island are being developed and made free from malaria; jungle areas are being cleared; and irrigation is being introduced. This may enable the island to support the increasing population.

Death of Obstetrician to the Royal Family.—Sir William Gilliatt, who was obstetrician to the Royal Family, died on Sept. 27 as a result of a traffic accident. He had been president of the Royal College of Obstetricians and Gynecologists and of the Royal Society of Medicine.

Cytological Diagnosis of Sex.—The claim of James (*Lancet* 1:202, 1956) that the sex of a fetus can be diagnosed from the examination of karyosomes in amniotic fluid cells has been confirmed by Sachs and co-workers (*Lancet* 2:795, 1956). They obtained amniotic fluid by puncture of the membranes and in the earlier months of pregnancy, with the exception of the third month, by abdominal puncture. The fluid was centrifuged, and the deposit stained on a slide with the Feulgen method, which is specific for desoxyribosenucleic acid. This is only present in the chromosomes and gives a clear staining of the karyosomes. The karyosome is longer in the cells of a female than of a male, and the percentage of cells with a karyosome at the nuclear membrane is greater. The figures are 4% in male cells and 38% in female cells. Dixon and Torr examined chromosomal sex differences in cells contained in oral smears (*Brit. M. J.* 2:799, 1956). Oral smears from 257 persons, representing a wide range of age and racial variation, were examined by Feulgen staining. In 162 male smears, no sex chromatin was seen, whereas, by contrast, in most of the 95 female smears between 30% and 50% of the cells counted contained a sex-chromatin mass. In the female smears, the sex chromatin was usually first seen in one of the first five cells counted. As this occurred with such regularity it was decided that a count of 25 cells from an oral mucosal smear was adequate for sex determination.

Histoplasmosis.—Prof. W. Symmers has described the first proved case of histoplasmosis in which infection was acquired in Great Britain (*Brit. M. J.* 2:786, 1956). Histoplasma capsulatum was isolated from a biopsy specimen taken from a patient who, like the other members of his household, had never been out of the British Isles. About a dozen cases have been reported in Great Britain, but, in each case, the patients had lived abroad in an area where histoplasmosis was endemic. In Symmers' patient, the only manifestations of the infection were enlargement of the cervical lymph nodes and a positive skin reaction to histoplasmin. H. capsulatum was found in cultures from one of the lymph nodes. No members of the patient's household reacted to intradermal histoplasmin, and the patient's hobbies and recreation did not expose him to any environment that has been incriminated as a source of infection.

Enzyme Tests for Detection of Glycosuria.—Hunt and co-workers reported on the use of glucose oxidase for the routine detection of glycosuria in diabetics (*Brit. M. J.* 2:586, 1956). The purified enzyme is now available commercially in testing preparations known as Tes-Tape and Clinistix. The former is a roll of test paper impregnated with glucose oxidase, *o*-toluidine, a vegetable peroxidase, and a yellow dye. When the strip is dipped into a liquid containing glucose, the oxidase in the presence of air converts it to gluconic acid and hydrogen peroxide, which with the peroxidase converts the *o*-toluidine into a blue oxidation product. This with the yellow dye gives a color, ranging from light green through dark green to dark blue, according to the amount of glucose present. A color scale is provided with Tes-Tape to indicate colors corresponding to 0, 0.1, 0.25, 0.5, and 2 gm. of glucose per 100 ml. of urine. Clinistix is a preparation in the form of separate strips of thick paper resembling book matches. No color scale is provided, as the test is purely qualitative. From tests on urine specimens from 174 diabetics known to be excreting glucose, from 43 patients excreting no glucose or only trace amounts, and from 46 normal subjects, it was concluded that both Tes-Tape and Clinistix are sufficiently accurate for the qualitative detection of glucose in urine. The limit of sensitivity is about 0.1 gm. per 100 ml. The advantage of these preparations is that no apparatus, boiling, or white tiles are necessary and that the test is specific for glucose; however, strict chemical cleanliness is necessary. Occasional false-positive tests were observed, but in no case did glycosuria go undetected. The authors are not satisfied that the preparations permit an accurate estimation of the amount of glucose present in urine. There was a significant difference in the amounts reported by different observers on the same urine specimens, and even greater discrepancies occurred when untrained observers read the results.

New Health Service Regulations.—The Minister of Health, after consultation with the representatives of the medical profession, has incorporated certain new regulations in the National Health Service code. These became effective on Oct. 1. The main amendments provide for (1) periodic reviews by executive councils of consents given to a physician to employ a permanent assistant; (2) a new procedure for identifying patients on a physician's list who are at a school or residential institution and, when they have gone away, for removing them from the list; (3) the abolition of back debits and back credits; (4) making a deputy to a physician responsible for his actions when both the deputy and

the physician for whom he is deputizing are on the same medical lists; (5) enabling executive councils to make arrangements for the treatment of a physician's patients when he is absent or disabled; and (6) increasing the fee payable to a physician for the treatment of temporary residents at certain types of institution.

Overpopulation.—Overpopulation of the world, famine, disease, and disaster are not inevitable according to Dr. C. B. Goodhart, who addressed the annual meeting of the British Association for the Advancement of Science. Man's fertility may be lowered by natural selection. Families of lower fertility but otherwise good qualities are more likely to survive. In the British peerage, wealth in women is associated with infertility. An heiress by definition comes of a family of low fertility, for otherwise there would be siblings or other relatives to share her wealth. Many noble families have become extinct by the marriages of the sons to heiresses whose riches were as great as their infertility. The unattractive wife of King Louis XV of France had 10 children, whereas the attractive Mme. de Pompadour, his mistress, despite all her wishes, had only one child, who died young. Many other human characteristics leading to success in life are associated with low fertility; this, in turn, usually results in a higher standard of living. Population increase is primarily a biological phenomenon. The arguments of Malthus were based on the assumption that man had a specific and constant rate of reproduction, which would be the same in the future unless artificially altered. This assumption is not necessarily true. The present rate of increase in the population is quite exceptional. For 99% of his history, man lived as a nomadic hunter and food collector. The densely settled agricultural and urban communities characteristic of the last few millenniums are a relatively recent development. We cannot assume that the high fecundity found in these dense and unhealthy aggregations of population is necessarily typical of the human species. Declining numbers are found not only in primitive peoples brought into contact with civilization but also in many of the most advanced nations. The conditions produced by civilization and a high standard of living may in themselves be unfavorable to fertility. Those qualities leading to success in man may have become genetically correlated with relatively low fecundity.

Fertility in Scotland.—The *British Medical Journal* of Sept. 8 contains an annotation stating that, as a result of the steady fall in the birth rate from 316 per 1,000 married women in the period 1860 to 1862 to 132 in the period 1950 to 1952, the average size of families in Scotland has fallen from 6 to 2.5 children. The decline in childhood mortality has compensated for only part of the decline in fertility. The infant mortality rate is now 25% of the rate of 50 years ago, and the death rate for children under 10 years of age is about 12% of the rate of 50 years ago. A recent publication of the General Register Office, Edinburgh, presents statistics showing that almost 20% of all the married women in a random sample have no children and that only 0.6% have 10 or more children. The number of women at 23 years of age with no children and the number with one child are about equal. By the time a woman is 24 years of age, the average size of her family exceeds one child, but not until she is 32 years old does the average exceed two children.

For marriages under two years' duration, the number of childless women exceeds the number of women with one or more children. One-child families are the most frequent for women who have been married two to five years, but after six years of marriage the two-child families predominate. For marriages of the same duration, the average size of the family decreases with the increasing age of the mother at marriage. When analyzed by social class of the husband, the size of the family rises from an average of 1.48 for social class 1 to 2.58 for social class 5. There is a wide range in the average size of the family classified according to the occupation of the mother: for example, 70% of married clerks, typists, and office workers have no children, while only 12% of charwomen and office cleaners are childless. However, over half the women in the former group had been married for less than five years, while over half of those in the latter group had been married for 15 or more years. Geographical differences in the average size of the family are small: the rural areas have the largest families (average size about 2.11) and the small towns the smallest (1.90).

Streptococci on the Umbilicus.—The *British Medical Journal* of Sept. 8 contains an article by Drs. Boissard and Eton and another by Drs. Kwantes and James who simultaneously conclude that many hitherto unexplained outbreaks of streptococcic infections in maternity hospitals can be traced to an umbilical source, and they make the plea that bacteriological investigation of the nursery should be carried out whenever a case of streptococcic infection is found in a mother or a member of the staff. There was no local sign of any infection in most of the infants whose cords were found to be infected. It is not surprising that the stump of the cord, consisting of dead tissue undergoing dissolution, should support the free growth of bacteria. What is surprising is that an infant with no acquired immunity and with only a few days' experience with bacteria of any kind should be able to keep virulent streptococci in check at the junction of dead and living tissue. These observations nevertheless show that the umbilicus can be a symptomless reservoir of such infection. Contaminated in the first instance probably by a nurse, it can evidently be the source from which the mother acquires a uterine infection and from which other babies in the ward acquire an umbilical infection. One effect of these findings must be that umbilical swabs be regularly included in those taken to determine the source of infection in puerperal fever.

No More Overtime in Mental Hospitals.—More than 26,000 male and female nurses in mental hospitals refused to work overtime after Oct. 1. The ban must worsen conditions already bad because of overcrowding and a shortage of staff workers. A last-minute effort to avert this will be made. The decision to ban overtime was taken by a vote of 399 to 381 and will continue until the demands of the Confederation of Health Service Employees are met in full. These include higher ordinary and overtime pay; a 44-hour week; and six weeks' annual leave, including bank holidays and weekly leaves. A 96-hour fortnight is the rule in both mental and general hospitals. The Industrial Court has rejected the confederation's request that overtime after 96 hours should be paid for at time and a quarter for the first two hours and time and a half thereafter. At present, overtime is paid for at the ordinary rate. Much overtime is worked and is popular with many employees as an additional source of income. Nurses commonly work 80 to 70 hours a week; many have broken down under the strain. Others have forsaken mental health work for other forms of nursing. Dissatisfaction is general throughout the service. The secretary of the confederation emphasized that no patient would be left uncared for because of the ban. Nurses will not be required to leave patients needing attention until a relief has arrived. While patients will not lose nursing care, they will be deprived of such things as entertainment, because no one will be available to supervise.

Eyeglasses Without Examination.—The harmful effects of eyeglasses bought in shops without an ophthalmologic examination or professional advice are being investigated. Results of the inquiry will be reported to the Minister of Health. Shop sales of glasses dwindled almost to nothing after the introduction of the National Health Service, which made it possible to obtain glasses free. However, since May, 1951, people have had to pay $2.80 and the cost of the frames. Again there is much indiscriminate buying. Glasses can be bought for as little as 28 cents a pair. Among those who buy their glasses from shops and peddlers are many old-age pensioners. Concern about increasing shop sales of eyeglasses was expressed in a resolution submitted at the Labor party conference in October that urged that plans be prepared for the next Labor government to stop this practice and reintroduce free glasses. The Guillebaud Committee on the cost of the National Health Service, in its report last January, recommended that, when it could be afforded, a substantial reduction in the charge for glasses should be given high priority.

THE LEISURE CORNER

SKIING AS WEEK-END RECREATION

"Travels in the mountains undertaken in the company of friends are the highest of all pleasures and the most charming of all delights of the senses are obtained. . . ." So wrote Conrad Gessner, physician of Zurich, Switzerland, in 1555. The peripatetic doctor did not mention skis as the model mode of "travels in the mountains," but it can be safely assumed he might have had them in mind, since men have used skis to journey in mountains for more than 4,500 years.

At any rate, millions of Americans, 400 years later, are taking the Swiss doctor's remarks to heart. Every week end, from November through April, depending on the weather, of course, the highways are filled with automobiles carrying skiers, young and old, to the snow-covered slopes; railroad stations resound to the joyful and enraptured shouts of athletes, aged 20 to 60, carrying skis and rucksacks like so many gay, brilliant banners.

These are the week-end athletes—office boy and office manager, factory hand and plant foreman, salesman and store executive—released by the shorter work week from the shackles of their jobs for long week ends. Two days a week they can be found shackled to two slim wooden boards, racing up and down snow-covered slopes to steep inclines with the abandon that is the distinguishing characteristic of their sport. Dangerous? A little, perhaps, but not so bad as a treacherous undertow or a fall from a horse, is the skier's retort. Difficult? Anything that can be learned on week ends, not necessarily consecutive, is not hard. Rugged? Persons in their 50's have been known to take up the sport for the first time and stay with it in their 60's.

Week-end athletes, of course, suffer one drawback—the uncertainties of the weather. In the summer they repeat the intonation of their childhood: "Rain, rain go away, come back another day." In the colder weather they look longingly to the skies for the gray clouds that spell the advent of snow. Physicians who can get away for several weeks at a time have a much better chance of ascertaining the truth of their ancient colleague's observation. Once they get the taste, the chances are they will become week-end athletes too. And since there are no age limits, skiing can become a family affair. Wife and children can easily fit in "the company of friends" to guarantee "the highest of all pleasures."

Mountains need not be high or overly rugged; sites are available for individual tastes and peace of mind. The only requisite is the desire. And as for the last, there is only one note of caution: once you get the desire, you never lose it. Nor need skiing be an expensive sport. It is only if you want it to be. However, it is not wise to stint on good equipment; poor equipment can be false economy.

Most important ingredients of your outfit are boots and bindings, since they are the links between skier and ski. Put on thick woolen socks before trying on the boots to make sure the boot will fit properly. Some ski experts even insist that you bring along your own socks for the fitting to make certain the boots will not feel too snug. As for the bindings, all-metal ones are considered the best, although some experts recommend a good grade of leather straps for beginners.

Skis, almost everyone agrees, should be of hickory wood. Other woods are unsatisfactory for various reasons, and metals and plastics have not been sufficiently tested to have won wide acceptance. Some experts say a ski must reach to the base of your thumb when you stand them erect; others insist weight must be considered. The latter advise a ski somewhat shorter than the base-of-thumb length. Good ski poles should reach from boot to armpit and be made of metal tubing or tonkin cane. Well-padded hand grips and good leather wrist straps are important.

Ski clothing generally is a matter of individual taste, but here the experts also have a word of caution. Designers for one of the foremost makers of ski clothing in the country advise that pants and jackets should be well fitted and tapered, yet full cut to permit freedom of movement. They say loose-fitting pants, for instance, tend to cause wind resistance. The material should be closely woven, smooth, and snow-repellent. Do not make the mistake of buying ski clothing for warmth, the experts add. Undergarments will supply warmth, but you must make sure they do not supply too much bulk as well. Then there are such incidentals as goggles, wax, mittens, sunburn preventives, and other items that individual skiers may like. Most of them are necessary, but none are too expensive.

Different conditions prevail in different parts of the country, which means that skiing techniques may vary from place to place. But no one has to become an expert in any or all types of skiing to enjoy the sport. No matter what time of life you begin, you have the rest of your active span of life to improve both style and technique—if you care, or if you have any style or technique to improve.

Of course, there are certain fundamental skills to learn. One school promises to teach skiing in a week. Whether you are interested in the Swiss school, or the Arlberg, or the Norwegian, or the American, it does not matter. Fundamentally there is one system of skiing. All schools are based on the snowplow or the snowplow turn. In the snowplow your skis form a reverse V to brake your momentum; in the snowplow turn, you turn right by shifting weight to the left ski, and left by shifting to the right ski. And above all, no matter what the school, the system, or the technique, you must learn to relax.

Since relaxation and leisure are inseparable, like ski and boot, what better way of combining both than by skimming through the dustless air of higher altitude, over the bluish luster of virgin snow, through wooded trails, enjoying the long, slow rhythm of great sweeping turns or knowing the enormous spray of powder snow thrown up by a jerked Christiania. And through it all courses the ecstasy and the strange intoxication of swift passage through the keen, sharp, clean, tangy atmosphere. Slalom!

MEDICAL FILM REVIEWS

Fractional Lumbar Epidural Analgesia: 16 mm., color, sound, showing time 12 minutes. Prepared by LeRoy W. Krumperman, M.D., Philadelphia. Produced in 1956 by Audio Productions, New York, for Sharp and Dohme Division of Merck and Company. Procurable on loan from LeRoy W. Krumperman, M.D., 3401 N. Broad St., Philadelphia 40.

The purpose of this film is to show a practical technique of performing lumbar epidural analgesia. The contents of the epidural tray are shown and described, and the value of this technique of regional analgesia for surgery as well as for a diagnostic and therapeutic block is pointed out. The technique of identifying the epidural space by using the "drop-sign" of Gutiurez is shown; also shown is the introduction of a polyvinyl catheter through the needle into the epidural space. By anatomic drawings, the film shows the proper position of the needle in the epidural space and also the polyvinyl catheter in the epidural space. The indications and contraindications for this form of regional analgesia are described, and there is also a comparison made between epidural and spinal analgesia, with the advantages and disadvantages of each technique pointed out. The over-all film is good; however, the advantages and disadvantages of other drugs and the other techniques for locating the epidural space should have been mentioned. The hazards of and the preparation for a reaction to a local anesthetic should have been discussed. The photography is good, and the film is recommended for surgeons, anesthesiologists, and members of hospital house staffs.

Dynamics of the Tubercle: In Vivo Observation of Pathogenesis and Effects of Chemotherapy in the Cloth Rabbit Ear Chamber: 16 mm., color, sound, showing time 28 minutes. Prepared by Robert H. Ebert, M.D., and William R. Barclay, M.D., University of Chicago. Produced in 1956 by Churchill Wexler Productions, Los Angeles, for and procurable on loan from Pfizer Laboratories, Chas. Pfizer and Co., Inc., Brooklyn 6, N. Y.

This excellent film shows the effect of the introduction of disease in normal tissue and the results of chemotherapy upon the disease. The early part of the film explains normal circulation in the rabbit ear and describes in detail progressive changes in the normal vessels, blood cells, and connective tissue after the introduction of the tuberculosis organisms in a primary infection and also the development of the tubercle in reinfection tuberculosis. The latter part of the film shows the effects of chemotherapy on the tubercle. This is an excellent teaching film for histology, physiology, and pathology, since it demonstrates (1) normal tissue, (2) the result of introduction of infection in normal tissue in the primary stage and reinfection stage, and (3) the effect of chemotherapy on the evolution of the infection. This film should be used not only in all medical schools but also in schools of nursing and as a part of the educational process of science students at the college level.

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

Dissecting Aneurysm of the Aorta with Neurological Involvement. E. N. Weaver. Virginia M. Month. 83:431-437 (Oct.) 1956 [Richmond, Va.].

The author describes five cases of dissecting aneurysm of the aorta in four men between the ages of 33 and 64 years and in a 55-year-old woman. Each of these patients had neurological changes consisting in four of paralysis of the lower extremities, right hemiparesis and a right homonymous hemianopsia, weakness and numbness of the right leg, and weakness of both legs respectively. The neurological changes, which were produced by ischemia of some part of the nervous system as a result of the aortic dissection, emphasized the dominance of neuropathology as the basis of the patients' symptoms. A dissecting aortic aneurysm should be considered in patients who experience sudden severe and unexplained chest, abdominal, back, or leg pain with bizarre radiations and associated neurological signs and symptoms. All five patients died, and autopsy was performed in four. Death occurred as a result of rupture of the aneurysm into the pericardium, the thoracic cavity, or the abdominal cavity. One patient had repeated ruptures and lived for almost five months from the time of onset of his illness. The importance of developing a clinical consciousness of this condition with early diagnosis is emphasized, since many of these lesions are amenable to treatment.

Clinical Consideration on Arterial Embolism and Valvular Misfunction. G. Micheli-Pellegrini and P. R. Lapi. Sett. Med. 44:344-349 (July 15) 1956 (In Italian) [Florence, Italy].

The authors studied arterial embolism in 895 cases of rheumatic valvular disease of the heart. Embolism was found in 38 patients (4.2%). Twenty-nine patients had cerebral embolism, 19 on the right side and 10 on the left side. Two had it in the left arm, one in the right arm, two in the bifurcation of the common iliac, four in the left leg, one in the right leg, and one in the mesentery. The patients were mostly between the ages of 40 and 50 years. There were 33 women and 5 men. It is possible that endocrinal and vegetative factors, the balance of which is less stable in women than in men, may play an important role in causing embolism. Physiological changes in genital function seem to influence the general course of heart disease. The authors noticed in the past history of five patients that the detachment of the embolus coincided with the premenstrual period. Arterial embolism was noticed mainly in patients with valvular mitral disease. Autopsy in five patients showed severe mitral stenosis. Embolism rarely occurred in the first 15 years of the heart disease. Bouillaud's disease was the type of rheumatic disease chiefly responsible for valvular misfunction.

A Study of Serum Lipoproteins in Normal and Atherosclerotic Patients by Paper Electrophoretic Techniques. W. P. Jencks, M. R. Hyatt, M. R. Jetton and others. J. Clin. Invest. 35:980-990 (Sept.) 1956 [New York].

Studies were made to test the large-scale application of two relatively simple methods for the estimation of electrophoretically separated serum lipoproteins by measurement of their cholesterol content and dye-binding capacity. The results of these two methods were compared with each other and with ultracentrifugal methods, the aim being to obtain further confirmation of the association of serum lipoprotein abnormalities with atherosclerosis. Both healthy and hospitalized control groups were used to lessen the possibility that any observed abnormalities might be the result of illness, medication, diet, or restricted activity rather than of atherosclerosis per se. A standardized technique for the estimation of serum lipoproteins separated by paper electrophoresis gave results comparable to those of cholesterol determinations on these lipoproteins and of ultracentrifugal analysis of lipoproteins at a density of 1.21. No appreciable difference in lipoprotein concentration or distribution, measured by paper electrophoretic techniques, was found between the serums of 68 healthy male Army officers and the serums of 65 patients hospitalized with diseases not associated with atherosclerosis or abnormalities in lipid metabolism. Analyses of serums from 77 men with atherosclerosis, as judged by a history of myocardial infarction, showed a significant drop in alpha lipoprotein and increase in beta lipoprotein, resulting in a decreased ratio of alpha to total lipoprotein in these serums as compared to those of the control groups. Elevations in total cholesterol and total lipid dye-binding capacity were less significant. The percentage of the total serum cholesterol in the alpha lipoprotein fraction was lower in serums from patients studied from zero to six months than in those studied more than six months after an acute episode of myocardial infarction. The electrophoretic distribution of serum proteins showed greater deviations from normal in the group of hospitalized patients than in the atherosclerotic group. Ultracentrifugal analysis of lipoproteins of Sf 12-20 were less often abnormal than were electrophoretic analyses of the ratio of alpha to total lipoproteins in serums from atherosclerotic patients.

Gastric Ulcers: Review of 100 Cases. J. H. Geddes, W. N. Downe and J. A. Taylor. Canad. M.A.J. 75:550-554 (Oct. 1) 1956 [Toronto, Canada].

One hundred patients with gastric ulcer were treated at the Westminster Hospital in London, Ontario, between 1948 and 1952. Thirty patients were treated surgically and 70 were treated medically. The reasons for operation in the surgically treated patients were suspected malignancy in 14, recurrent ulcer in 13, and hemorrhage in 3. With the exception of six, all had subtotal gastrectomies. Only one of the 30 patients treated surgically was found to have carcinoma of the stomach. All medically treated patients were followed up for from two to seven years and none of them had any evidence of gastric malignancy. Twenty of the 100 patients have died since the diagnosis of gastric ulcer was made, and none of them died of gastric neoplasm. These results seem to vindicate the authors' present method of treatment for gastric ulcers, consisting of three to six weeks of intensive medical management in hospital in an attempt to arrive at an opinion concerning the question of malignancy of the ulcer. Clinical and radiological evidences of healing were considered the most important factor in deciding the nature of the ulcer. Other aids employed were the degree of gastric acidity, gastroscopic appearance, and cytology of gastric washings, when available. At the end of three weeks patients were again examined roentgenologically, and if healing was complete the ulcer was considered benign. If healing was incomplete, medical treatment was continued for three more weeks, followed by another barium meal. If the latter showed continued evidence of ulceration, the ulcer was considered malignant and surgery recommended. All patients with ulcers deemed benign were advised to have a barium meal every three to six months for two years.

It would appear that, with careful evaluation of a gastric ulcer in a patient hospitalized for a period of from three to six weeks, an error of 3% or less can be expected. Partial gastrectomy, the surgical treatment of choice for gastric ulcers, has a comparable mortality rate and in addition a definite morbidity of 10%. It is concluded that treatment of patients with gastric ulceration should be individualized, that surgery is not warranted for all patients with gastric ulcer, and that as a rule it should not be carried out before an earnest and careful attempt

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has been made to determine whether benignity or malignancy exists. Surgery should be carried out as soon as possible in all patients with recurrent ulcer, ulcer on the greater curvature, pyloric obstruction, hemorrhage, and perforation.

The Superior Vena Caval Syndrome: Report of 21 Cases. E. A. Calkins. Dis. Chest. 30:404-411 (Oct.) 1956 [Chicago].

Twelve men and nine women between the ages of 41 and 83 years with superior vena caval obstruction were admitted to the Los Angeles County General Hospital between 1947 and 1954. Clinical evidence of superior vena caval obstruction consisted of swelling of the neck, face, and arms and extensive venous collateral circulation over the chest and abdomen with downward flow of blood. In addition, 9 of the 21 patients had shortness of breath and cyanosis of the upper extremities. Arm venous pressure readings were obtained in eight patients with a range of from 250 to 800 mm. sodium chloride solution and an average of 386 mm. Only four pressure readings were obtained from the patients' lower extremities, showing an average of 165 mm. with sodium chloride solution. Arm-to-tongue circulation time averaging 34 seconds was determined with the aid of dehydrocholic acid (Decholin) in six patients. Arm-to-lung time averaging seven seconds was determined with the use of ether in three patients. In four patients angiograms illustrated superior caval or innominate obstruction. The superior vena caval syndrome was caused by bronchogenic carcinoma in 11 patients, by aortic aneurysm in 2, by substernal thyroid in 2, and by undiagnosed mediastinal tumors, nodes, or granulomas in 6. Fifteen patients died, 11 as a result of bronchogenic carcinoma. Six with remission of symptoms or no progression were discharged.

A review of the literature suggests that the major causative factor is bronchogenic carcinoma, which may involve the superior vena cava in from 10 to 15% of the patients, with a generally unfavorable prognosis. With increased knowledge and use of vessel grafting the prognosis is brighter for those in whom the obstruction of the superior vena cava is not caused by a malignant tumor or an aortic aneurysm. Some definite trends were noticed in the author's small series of cases. In contrast to the reports in the literature the predominance of men in the ratio of men to women was reduced from 75% to 57%. The age of the patients appeared to increase and so did the incidence of bronchogenic carcinoma as a causative factor. The average venous pressure in the arms may exceed that in the legs by more than 200 mm. sodium chloride solution.

131-Labeled Fat in the Study of Intestinal Absorption. J. M. Ruffin, W. W. Shingleton, G. J. Baylin and others. New England J. Med. 255:594-597 (Sept. 27) 1956 [Boston].

Characteristic and reproducible curves of blood levels of radioiodine (I^{131}) have been demonstrated with the use of both radioactive-tagged albumin and radioactive-tagged fat. This method of study was applied to patients with a variety of disorders of the gastrointestinal tract to determine whether their radioactive blood levels and fecal content differed significantly from those found in normal persons. A cold emulsion and a "hot" emulsion were prepared. The cold emulsion consisted of 200 ml. of peanut oil, 200 ml. of water and 15 ml. of Tween 80. The "hot" emulsion consisted of 45 ml. of peanut oil, 5 ml. of I^{131}-labeled glyceryl trioleate (2.0 mc. of I^{131}), 50 ml. of water, and 4 ml. of Tween 80. Each emulsion was prepared by mixing of the ingredients in a Waring blender for 15 minutes. Each patient, in a fasting state, was given a test meal consisting of the following: the volume of "hot" emulsion that contained 25 μc of I^{131} to which was added enough cold emulsion to make a total of 1 ml. per kilogram of body weight. Twenty grams of barium sulfate was added to the test meal, and the entire contents mixed. The subject drank the test meal. The container was rinsed twice with 50 ml. of tepid water, which was likewise ingested. The container was assayed for residual I^{131}. Twenty drops of Lugol's solution was given immediately after the test meal. Two milliliters of venous blood was withdrawn at hourly intervals for six hours after ingestion of the test meal. Each sample was placed in a separate tube and assayed for I^{131} content in a scintillation crystal-well counter.

The 180 patients tested with the labeled fat included 44 with functional gastrointestinal disturbances; 57 with gastrointestinal diseases (including pancreatitis, carcinoma of the pancreas, sprue, enteritis, colitis, and hepatic cirrhosis); and 79 who had been operated on for peptic ulcer. In the group of patients with functional gastrointestinal disturbances, the blood levels and fecal excretion were within normal limits, while patients who had disease of the small intestine, regardless of cause, invariably had profound lowering of their blood levels and marked increase in radioactive content of the stool. The patients with sprue in clinical remission had completely normal blood and stool values, pointing to the reversibility of the pathological process. Patients with disease of the colon only had normal absorption. This was also true of patients with cirrhosis of the liver. The evidence in patients with disease of the pancreas points to faulty digestion rather than to an intrinsic error of absorption; 12 of the 13 patients with carcinoma of the pancreas had abnormal levels. Fifty-three per cent of the patients who had undergone gastric surgery for peptic ulcer showed significant lowering of the blood curves and increase in radioactive content of the stool. It is well known that appreciable weight loss is fairly common in postresection and postvagotomy patients; these findings suggest that one of the factors causing weight loss in this group of patients is impaired fat absorption.

Superior Vena Cava Draining into Left Atrium: Another Cause for Left Ventricular Hypertrophy with Cyanotic Congenital Heart Disease. H. Tuchman, J. F. Brown, J. H. Huston and others. Am. J. Med. 21:481-484 (Sept.) 1956 [New York].

A 15-year-old boy was hospitalized in February, 1955, complaining of fatigue and unexplained fever. In October, 1954, his physician had found that polycythemia was present. In February, 1955, the patient appeared to be moderately plethoric with cyanosis of the acral parts. Down-curving of the finger nails without actual clubbing was noted. The conjunctival and retinal vessels were engorged. The left border of cardiac dulness was at the midclavicular line. The liver was palpable 3 cm. below the costal margin, and the spleen was just palpable. Cardiac catheterization revealed a superior vena cava that drained into the left atrium. The impression was that the patient had a single vascular anomaly in which the superior vena cava entered directly into the left atrium. Surgical exploration confirmed this. The aorta and the left ventricle were enlarged. The right atrial appendage was hypertrophied and dilated. Within the pericardium and extending upward from the cephalic end of the right atrium was fibrous remnant of the normal superior vena cava. The patient died 20 hours after the operation.

Postmortem examination confirmed the diagnosis and failed to reveal any other congenital cardiac anomaly. The case is thought to be of interest because it represents another type of cyanotic cardiovascular anomaly producing left ventricular hypertrophy and because the quantity of shunt as calculated here confirms the existing impression that about one-third of the venous return is via the superior vena cava and about two-thirds via the inferior vena cava. The diagnosis should be easily available to all who have access to cardiac catheterization and angiocardiography, and correction by surgery is feasible.

Episodic Stupor Following Portacaval Shunt: Observations on Etiology and Therapy. C. J. Fisher and W. W. Faloon. New England J. Med. 255:589-594 (Sept. 27) 1956 [Boston].

A 58-year-old man was first hospitalized with hematemesis, and a diagnosis of portal cirrhosis with bleeding esophageal varices was made. He had a history of chronic alcoholism associated with a poor dietary intake for many years. A splenorenal shunt was performed. Six months later he was readmitted with gastrointestinal bleeding, and x-ray study again revealed esophageal varices. A portacaval shunt was performed. Twelve episodes of coma or deep stupor were observed in this patient. They could be related to intolerance to more than 25 gm. of dietary protein ingested orally, to protein hydrolysate infusions, or to oral administration of ammonium chloride. The sequence of the development of coma included the stages of flapping tremor of the outstretched extremities, usually associated with mental confusion, gradually increasing stupor, and coma. During recovery the sequence of events was reversed.

His mental status, even when he was "alert," was markedly abnormal. No clear-cut correlation between the clinical condition and the venous-blood ammonia levels was observed. Neomycin therapy resulted in marked reduction in blood ammonia levels and enabled this patient to ingest a regular hospital diet containing approximately 90 gm. of protein.

Stable and Brittle Diabetes. J. G. Alivisatos and E. P. McCullagh. Am. J. Med. 21:344-357 (Sept.) 1956 [New York].

There are patients with long-standing diabetes in whom the blood sugar values are consistently fluctuating, in spite of attempts to obtain normoglycemic control, and who nevertheless have only very slight degenerative complications. The authors believe that this is due to uncertainties as to definition of the term "control" and to the failure to recognize the existence of two distinct types of diabetes mellitus, the stable and the brittle. They apply the term stable diabetes to patients who are insulin-insensitive and brittle diabetes to those who are insulin-sensitive. Another distinct metabolic feature of patients with brittle diabetes is that ketosis develops rapidly and repeatedly despite attempts to establish normoglycemic control. If insulin is not administered in adequate doses, diabetic coma will develop. Ketosis indicates increased catabolism of fat. These disturbances in the carbohydrate and fat metabolisms in patients with brittle diabetes suggest that this type of diabetes is a separate metabolic entity. This study was undertaken to ascertain whether or not other clinical or biochemical features distinguish brittle from stable diabetes and whether the incidence of late degenerative complications is different in these two groups of patients. One hundred seventy-two patients were studied, but only 149 fulfilled all the criteria for classification in one or the other of the two groups. There were 70 patients with brittle diabetes and 79 with stable diabetes. When distribution curves of the over-all blood sugar values were plotted, it was found that patients with brittle diabetes had a V-shaped curve indicating that these patients have a high frequency of blood sugar values in the two extreme ranges, the very low (less than 120 mg. per 100 cc.) and the very high (above 200 mg. per 100 cc.). In patients with stable diabetes the blood sugar curve is a descending line. Degenerative complications were more frequent in patients with stable diabetes than in those with brittle diabetes. The incidence of severe diabetic retinopathy was low in adult patients with brittle diabetes of long standing. Patients with stable diabetes with poor control showed a significantly higher incidence of late degenerative complications than patients with stable diabetes with good control.

Treatment of Severe Tetanus with d-Tubocurarine Chloride and Intermittent Positive-Pressure Respiration. A. C. Smith, E. E. Hill and J. A. Hopson. Lancet 2:550-552 (Sept. 15) 1956 [London, England].

Intermittent positive-pressure respiration in association with some method of preventing spasm is an advance in the treatment of severe tetanus. The patient presented, a 7-year-old boy, had an especially severe form of tetanus. He had been cut on the forehead by a sharpened stick used as an arrow. His doctor treated the wound, which was superficial, but gave no antitetanic serum because of an allergic reaction to a dose of serum given 18 months before. The wound became infected and was treated with penicillin and aureomycin. Four days after the injury the right side of the patient's face became stiff and trismus developed. The patient was treated for 26 days with paralysing doses of curare (up to 640 mg. in 24 hours to a total dose of 7,640 mg.), and respiration was maintained by intermittent positive pressure from a Radcliffe respiration pump. Chloral hydrate was given to prevent any memory of the period. The patient made a complete recovery.

The d-tubocurarine was chosen as the relaxant for two reasons: 1. Absolute muscle relaxation can always be obtained if enough curare is given. 2. Curare has been successfully used in other cases. The standard dose of curare in this patient was 15 mg. given intravenously, and this dose abolished all muscular movement for a time. Spasms, modified to myoclonic twitching, recurred after from 20 to 30 minutes, and more curare was given when these spasms became obvious. The authors gained the impression that the occurrence of even these modified spasms adversely affected the patient's general condition, and they would probably be even more lavish with the dosage of curare in a future case. The diet was based on an intake of 72 oz. of milk daily with additional glucose and Casilan to provide 1,750 calories. The high-protein diet usually given to these patients was not given, because this patient's blood-urea level never fell below 50 mg. per 100 ml. The patient's voracious appetite after normal feeding was resumed suggests that this calorie intake was insufficient. Penicillin and streptomycin were given for the first week against the causal organism and prophylactically against chest complications. Sulphadimidine in small doses was given for the rest of his illness and, in association with physiotherapy and changes of posture, controlled his chest infection. Promethazine was given to minimize allergic reactions.

Infection of Volunteers by a Virus (A. P. C. Type 1) Isolated from Human Adenoid Tissue. A. T. Roden, H. G. Pereira and D. M. Chaproniere. Lancet 2:592-596 (Sept. 22) 1956 [London, England].

A strain of type 1 APC (adenoidal-pharyngeal-conjunctival) virus was administered by nasal instillation to 11 volunteers. Garglings taken on the second, fourth, and sixth days after the instillation were examined for the presence of type 1 virus, which was recovered from none of the volunteers on the second day and from four of them on the fourth or sixth day. Acute pharyngitis developed on the fourth and fifth days in two of the volunteers from whom the virus was recovered. The remaining volunteers showed no clinical signs of infection. Paired serums were tested for neutralizing and complement-fixing antibodies for APC viruses of tyypes 1 to 6. Neutralizing antibodies for type 1 virus were not detected in the preadministration serums of any of the four volunteers from whom the virus was subsequently recovered but were present to varying titers in the preadministration serums of the remainder. All volunteers from whom the virus was recovered showed definite increases in neutralizing antibodies for the homologous type and variable responses to the heterologous types. Three volunteers from whom no virus was isolated showed increases in neutralizing antibodies. Rises in complement-fixing antibodies were observed only in the group of volunteers from whom virus was recovered and were greatest in the two volunteers who showed clinical evidence of infection.

Polycythemia and Hypernephroma. E. Noe. Nord. med. 56: 1164-1165 (Aug. 18) 1956 (In Norwegian) [Stockholm, Sweden].

In eight of the nine previously published cases of polycythemia and hypernephroma the finding of hematuria made possible the diagnosis of renal tumor during life. In the three patients operated on the polycythemia disappeared after nephrectomy. The polycythemia is thought to be secondary to the renal tumor. There is no clearly formulated theory as to the mechanism in this connection. In the case reported, in a man aged 55 with pleural exudate, there were no symptoms from the urinary tract to indicate urography. The diagnosis of polycythemia was based on the hemoglobin, red blood cell, and thrombocyte values, together with the typical sternal punctate. Cerebral symptoms that set in were ascribed to cerebral thrombosis, and anticoagulant treatment was applied. The patient died in coma and hyperthermia. Autopsy revealed a tumor of the right kidney and tumors of similar appearance in the right pleura and right cerebral hemisphere. The microscopic picture showed hypernephroma. The pleural exudate proved to be an expression of pleural metastasis of the hypernephroma.

Pneumoperitoneum in the Management of Esophageal Hiatus Hernia: A New Diagnostic and Therapeutic Procedure. B. Maisel, W. Cooper and F. Glenn. J. Am. M. Women's A. 11:299-315 (Sept.) 1956 [New York].

Pneumoperitoneum was used as a new diagnostic and therapeutic procedure in five patients with esophageal hiatus hernia. The pneumoperitoneum established the differential diagnosis between angina from coronary arterial insufficiency and angina produced by hiatus hernia and also between dyspepsia caused by gallbladder disease and dyspepsia due to hiatus hernia. The

pneumoperitoneum controlled hemorrhage, vomiting, rumination, and dyspepsia caused by hiatus hernia. It is induced in the following manner: The patient is placed in the supine position. The abdomen is shaved and prepared with three applications of zephiran. A point midway between the left costal margin and the umbilicus is infiltrated with 2% procaine solution. A 19-gauge needle, 1.75 in. long, attached to a 10-cc. syringe, is introduced into the abdominal wall to a point where the anterior rectus sheath is encountered. A needle guard or a clamp is adjusted to the needle to permit safe advancement for another 1.5 cm. through the rectus muscle, the posterior rectus sheath, and the peritoneum. As the needle passes through the peritoneum, the patient feels a slight sticking pain. Five cubic centimeters of novocain is introduced into the peritoneal cavity to test the free flow and to make certain that the needle tip is within the peritoneal cavity. A three way stopcock is attached, and small amounts of room air are introduced to test the free flow into the peritoneal cavity. The 10-cc. syringe is replaced by one that holds 50 cc., and about 1,000 cc. of air is injected. Codeine phosphate is given every four hours for four doses to control the shoulder pain caused by the air beneath the diaphragm.

The peritoneum proved of particular value in aged patients with hiatus hernia. It did not produce recognizable interference with the cardiopulmonary function and did not complicate the operative management of these patients. On the contrary, the great amount of space beneath the stretched and elevated left diaphragm facilitated the repair of the diaphragm and the manipulation of the stomach, esophagus, spleen, and left lobe of the liver. Hiatus hernia may cause left flank pain, clinically indistinguishable from renal pain. The elderly patient with a symptomatic hiatus hernia may be treated on an ambulatory basis in a hiatus hernia pneumoperitoneum clinic, provided the initial injection of air is given in the hospital under close supervision. The clinical course and the signs, symptoms, diagnosis, and pathological changes of esophageal hiatus hernia are reviewed. The authors suggest that the development of paraesophageal and sliding hiatus hernia can be attributed to the loss of the normal vis-a-tergo of the tissues at the esophageal hiatus and the effects on the stomach of a rising and falling intrathoracic pressure associated with coughing, sneezing, and defecation. Hiatus hernia is often associated with chronic cholecystitis, cholelithiasis, and peptic ulcer.

Treatment of Uremic Nausea and Vomiting with Chlorpromazine (Largactil). P. Eilersen. Ugesk. læger. 118:933-934 (Aug. 16) 1956 (In Danish) [Copenhagen, Denmark].

In Bispebjerg Hospital intractable nausea and vomiting in 21 patients with uremia due to chronic nephritis, nephrosclerosis, or chronic pyelonephritis were treated by peroral administration of Largactil. The dosage was 25 mg. four times daily except in two instances, in which the dosage was 50 mg. four times daily. The symptoms ceased in nine patients, five were improved, and in seven there was no change. Two of the nine patients had been greatly troubled by hiccups, which ended at once on the Largactil treatment. The appetite was improved in all the improved patients. In spite of subjective improvement, the blood urea level was not reduced during the period of treatment. Nine patients with cancer metastases and four with other diseases were also treated with chlorpromazine because of nausea and vomiting. In four of the first group the symptoms disappeared entirely, while three were improved and two unchanged; in three of the second group the symptoms ceased, and the fourth patient was improved. While no side-effects of chlorpromazine were seen, the substance should, on account of the side-effects described in the literature, be reserved for the treatment of continuous nausea and vomiting in incurable patients.

Herpes Zoster and Liver Diseases. W. Siede. Deutsche med. Wchnschr. 81:1401-1402 (Aug. 31) 1956 (In German) [Stuttgart, Germany].

Siede reports on seven patients in whom herpes zoster occurred in association with liver disorders. The liver was more or less enlarged and its consistency increased in all seven patients. Liver biopsy in two patients revealed the histological characteristics of involvement of the hepatic mesenchyma, with proliferation and chronic inflammatory infiltration of the periportal tissues. This process also involved some of the peripheral lobules. The stellate Kupffer's cells were increased. The hepatic cells showed a granular or vacuolated protoplasm, and here and there a cell membrane and nuclear synthesis. The protein tests indicated pathological changes, and electrophoresis revealed a constellation of the protein fractions characteristic of hepatic impairment. Liver-function tests carried out during the acute stage also indicated a pathological condition. Only one of the patients was definitely jaundiced, but three were subicteric. In five of the patients the hepatitis subsided within weeks; in one it persisted for eight months; and the seventh still has signs of chronic hepatitis after two years.

Herpes zoster is apparently an infectious disease caused by a virus. The question arises whether the concurrence of herpes zoster and hepatitis in the cases presented was fortuitous or whether there was an etiopathogenetic relationship. In some of the patients the herpes zoster appeared in the segments that correspond to the sympathetic innervation of the liver. This might suggest that the virus hepatitis produced a site of lessened resistance; however, this would presuppose that the hepatitis preceded the herpes zoster, and this occurred in only one of the patients, whereas in the others the appearance of the two disorders coincided. The author believes that both diseases can be caused by the same virus. A number of virus diseases are known to cause disorders in several organ systems. As a typical example he mentions glandular fever, which involves not only the lymphatic apparatus but occasionally also the liver and the central nervous system. The same applies to primary atypical pneumonia. More recently it has been observed that the virus diseases of the central nervous system may show the same behavior. Thus, involvement of liver and spleen and even hepatitis with jaundice has been observed in poliomyelitis. When hepatitis appears concurrently with herpes zoster, it is possible that a zoster virus with hepatotropic properties is the cause.

Bleeding Peptic Ulcer: A Clinical Study of 311 Cases. A. Aldman and S. Wallensten. Acta med. scandinav. 155:205-222 (No. 3) 1956 (In English) [Stockholm, Sweden].

Four hundred five men and 108 women between the ages of 30 and 80 years with bleeding gastroduodenal ulcers were treated at the medical and surgical departments of Serafimerlasarettet in Stockholm, Sweden, between 1942 and 1953. Two hundred thirty of the 311 patients had mild hemorrhage and 281 severe hemorrhage. Hemoglobin and red blood cell determinations were used as criteria of the seriousness of the hemorrhage. Patients with a drop of hemoglobin to 50% or less and a red blood cell count of 2 million or less were considered as having severe hemorrhage and all the others as having a mild hemorrhage. The seriousness of the hemorrhage and the measures to be taken were determined largely by the volume and the rate of bleeding. The type of the ulcer, the age of the patient, and the duration of the condition seemed to be of less importance with respect to prognosis. The patient's general condition at the time of admission or at some other arbitrarily chosen time did not provide any reliable basis for assessing the prognosis.

Conservative therapy was indicated in most of the patients. There was a gradual increase in the number and the volume of blood transfusions in the course of the later years of the 10-year period. Partial gastrectomy was performed only in 22 patients whose lives were threatened by the hemorrhage despite generous blood transfusions. X-ray examination was performed immediately on admission in 57 patients with bleeding ulcers. In 41 patients it revealed a niche in the duodenum or stomach from which the hemorrhage was believed to originate. Deformation of the duodenal bulb suggested the presence of a bleeding ulcer in 10 patients. There were only six patients in whom the roentgenograms did not give any information with regard to the source of the bleeding. In 45 of the 57 patients the x-ray examination had to be performed with the patient in recumbent position; in none of them was the hemorrhage increased by the x-ray examination.

Twenty-three of the 311 patients died, a mortality rate of 4.5%. Only one of the 230 patients with slight hemorrhage died, but 22 (7.8%) of the 281 patients with severe hemorrhage died. With more abundant blood transfusions the mortality rate was reduced from 7% during the period from 1942 to 1945 to 3% during that from 1950 to 1953. The mortality rate in the

patients subjected to partial gastrectomy also decreased with the introduction of modern shock therapy and improved techniques of anesthesia. In patients with massive hemorrhage the blood lost should be replaced as rapidly as possible by ample blood transfusions; if despite this measure the bleeding does not stop and the life of the patient is threatened, surgical intervention should be considered and it should be performed as soon as possible after the onset of the hemorrhage. Speedy surgical intervention is particularly advisable in patients over 60 years of age.

Pseudomembranous Enterocolitis and Antibiotics. C. R. Newman. Ann. Int. Med. 45:409-444 (Sept.) 1956 [Lancaster, Pa.]

Newman discusses pseudomembranous enterocolitis on the basis of many literature reports, and he describes the histories and autopsy studies of 12 patients with this disease observed in several small hospitals. Pseudomembranous inflammation of the intestine has been recognized for over a century, but during recent years there has been an apparent increase in its incidence. There is disagreement regarding the role of antibiotics in the production of this condition. A wide variety of causes, such as inorganic or metabolic poisons, bacterial infection, or mechanical factors, may play a part in it. Antibiotics appear to play a significant part in its development in many instances. They cannot, however, be solely responsible for all cases. Multiple factors are probably responsible, even in cases in which antibiotics have been administered. Either superinfection or the development of antibiotic-resistant organisms appears to be the greatest hazard in the use of the antibiotics. Superinfection results from a disturbance in the normal bacterial flora of the body cavities. The reciprocal inhibitory effect is therefore destroyed or lessened. Superinfection may involve the same organ of the body in which the primary infection occurred or a different one. Organisms hitherto unlikely to produce serious disease may occasionally cause a secondary infection more serious than the primary disease and may sometimes cause death. These secondary infections respond poorly to known antibiotics. They occur most frequently from two to five days after initiation of antibiotic therapy, the patient appearing to have a relapse after an initial period of improvement. Frequent cultural studies are necessary to foresee or promptly recognize a serious superinfection.

There is evidence that micrococci (staphylococci) play a major role in the development of severe pseudomembranous enterocolitis, because they are much more adaptable to antibiotics than is the normal intestinal flora. Carriers in a community or hospital where many patients have been treated with antibiotics are probably the source of these resistant organisms. The micrococcic enterotoxin very probably leads to the formation of a pseudomembrane by its direct irritant action and presumably also produces generalized systemic effects. Although erythromycin offers a great deal of help in treatment, micrococci seem gradually to become resistant to this drug also. Enterocolitis should be thought of whenever a relapse occurs during an illness, after injury, or after an operation, particularly when antibiotics have been used. If diarrhea, paralytic ileus, fever, dehydration, loss of blood volume, and collapse are present, vigorous treatment is necessary. Reports indicate a rising index of suspicion, inasmuch as more cases are being diagnosed before death, and early treatment will doubtless produce better results. Efforts should be made to prevent the enterocolitis that is related to the use of antibiotics by (1) preventing the development of organisms that are resistant to antibiotics and (2) by detecting resistant organisms before severe untoward reactions occur.

The Importance of the Fractional Serum Bilirubin Determination in Clinical Medicine. C. J. Watson. Ann. Int. Med. 45:351-368 (Sept.) 1956 [Lancaster, Pa.].

The observations of Hijmans van den Bergh on the essential difference between the prompt direct and the delayed or indirect reacting fractions of the serum bilirubin are supported by recent observations, especially those of Cole and Lathe on the polar, or water-soluble, and nonpolar, or water-insoluble, character of the two types. The hitherto undescribed bilirubin sulfate is a polar compound exhibiting a prompt direct diazo reaction. The ease with which nonpolar, crystalline bilirubin can be isolated from sources such as bile, in which the initial behavior is almost entirely polar, is more in accord with a complex than an intrinsic molecular difference. The validity of measurement of the direct reacting bilirubin at one minute deserves more emphasis. Measurement at 30 minutes includes significant fractions of the delayed, indirect, or nonpolar bilirubin. This is well demonstrated when the values at 1 and 30 minutes and the total (after alcohol), obtained with serum from patients with uncomplicated hemolytic jaundice, are compared with the amounts of polar and nonpolar bilirubin from the same samples, separated by reverse phase chromatography. The correspondence between one-minute and polar bilirubin is excellent. The 30-minute direct bilirubin, however, clearly includes nonpolar bilirubin.

During the last 10 years the fractional serum bilirubin determination, one-minute and total, has been used routinely in the University of Minnesota Hospital and the Minneapolis Veterans Hospital. The author emphasizes that the experiences accumulated during these 10 years with the determination of one-minute and total bilirubin and bilirubin ratios in relation to the clinical problems of jaundice, liver and biliary tract disease, and anemia, has fully confirmed the usefulness of this fractionation. The following points are cited as evidence that the fractionation often enhances the value of the serum bilirubin studies. 1. The one-minute bilirubin is often increased significantly within a normal value for total bilirubin. This has been observed especially in patients with early hepatitis, cirrhosis, common-duct stone, and hepatic carcinomatosis. The finding is of value in revealing an abnormality and, while not differential in itself, often points to the presence of disease of the liver or biliary tract. 2. Low bilirubin ratios in patients with elevated total serum bilirubin are indicative of retention jaundice in varying degree. The lowest ratios (<20%) are characteristic of hemolytic disease or constitutional hepatic dysfunction of the Gilbert type. The Dubin-Johnson type of jaundice and hepatic dysfunction generally exhibits ratios above 40%, most often in the range characteristic of ordinary regurgitation jaundice. 3. While the majority of patients with jaundice due to parenchymal liver disease have bilirubin ratios in the same general range as those found in cases of biliary obstruction (45 to 80%), there is a significant number of patients with diffuse liver disease in whom ratios below 40% are encountered. In the range of 35 to 40% there is small likelihood of confusion with (benign) biliary obstruction, and below 35% almost none.

SURGERY

Mitral Valvotomy: A Progress Report. R. W. D. Turner and H. R. L. Fraser. Lancet 2:525-531 (Sept. 15) and Lancet 2: 587-592 (Sept. 22) 1956 [London, England].

The first 250 patients from the cardiac department of the Weston General Hospital, Edinburgh, who were subjected to mitral valvotomy were analyzed with regard to various factors that may influence the operative result. These patients were all followed for more than 12 months: 202 for more than two years, 116 for more than three years, 37 for more than four years, and 9 for more than five years. Ninety-seven per cent had either tight (finger-tip) or fairly tight (terminal phalanx) stenosis. The ages of the patients ranged from 16 to 60, and 29 were aged more than 50. Forty-four per cent had auricular fibrillation, 27% had calcification of the mitral valve, and in 19% an intracardiac clot was found at operation. Two hundred fifty other patients with mitral stenosis were seen at about the same time and not advised to have an operation, because their condition was either too mild, too severe, or complex. The electrocardiographic signs of right ventricular hypertrophy are summarized, and the value of right-side V leads is pointed out. In association with signs of uncomplicated mitral stenosis evidence of right ventricular hypertrophy invariably indicated that the stenosis was sufficiently severe to warrant operation. Some of the radiological aspects of mitral disease are discussed, and emphasis is laid on the significance of the transverse lines, which are believed to indicate distended lymphatics. Cardiac catheterization is rarely required in the assessment for operation. The operative mortality was 8%. In patients aged less than 50, even with auricular fibrillation and moderate enlargement, it was 3%. There have been only two deaths in the last 100 cases. Seven patients died from 1 to 30 months after operation.

The results were good or very good in 70% and fairly good in 10% of the patients. Analysis of the poor results revealed that systemic embolism, inadequate valvotomy, and traumatic mitral incompetence were the surgical factors concerned. The larger the heart the less likely is a good operative result to be achieved or maintained, and the least hopeful combination is a large heart with auricular fibrillation and without electrocardiographic evidence of right ventricular hypertrophy. Auricular fibrillation, enlargement, calcification of the valve, and intracardiac clot are frequent in patients over 30; consequently the operative risk is greater and the proportion of good results smaller. Nevertheless, a good result was obtained in 17 of 29 patients aged more than 30 and in 7 of 8 patients without these adverse factors. The incidence of auricular fibrillation increases with age and with heart size. The mitral valve was calcified in 27% of the patients who came to operation. Its incidence increased with age and was greater in males. Disadvantages of calcification are that effective splitting of the commissures may be impossible and attempts to achieve it increase the operative risk; good function of the valve may not be achieved despite good splitting of the commissures; and calcific embolism may take place into the systemic circulation. Despite these facts good results were obtained in more than half the patients with severe calcification. Aortic stenosis does not contraindicate mitral valvotomy for mitral stenosis, because aortic valvotomy can be carried out at the same thoracotomy. Severe cardiac cirrhosis of the liver contraindicates operation. In pregnancy operation is advised only if it is clear from the history that there was progressive dyspnea before pregnancy and that valvotomy would have been indicated in any event. Although the operative result is largely determined by the local pathological changes in the mitral valve, most patients are still being referred for operation after the optimal time has passed. Operation should be considered whenever symptoms are progressive and should be carried out unless contraindications are present.

Surgical Treatment of Cancer of the Thyroid. H. A. Kingsbury. Am. Surgeon. 22:847-856 (Sept.) 1956 [Baltimore].

Ninety-one patients with histologically proved thyroid cancer were treated at the Roosevelt Hospital in New York during the 25-year period from 1930 to 1955. Six patients could not be traced after discharge from the hospital. The remaining 85 have been followed up for periods of up to 23 years. The 91 patients were operated on by 20 different surgeons and a number of residents. The extent of operation varied with the attitude of the surgeon in charge. Among 38 patients with papillary adenocarcinoma who have been followed up for from 1 to 23 years since operation, 3 are known to have died of thyroid cancer. Two of the deaths occurred seven years after the primary operation. Of 23 patients with the diagnosis of follicular and alveolar adenocarcinoma, 4 have died. This includes three patients in whom the disease was far advanced at the time of surgery. One patient was lost to follow-up. There were two deaths among nine patients with Hürthle cell carcinoma. One patient died 13 years after the primary operation. The other had generalized metastases at the time of operation and died two months later. Among seven patients with solid adenocarcinoma, five were in an advanced stage of the disease and received palliative treatment only. Six of the seven died. Of 10 patients with giant and spindle cell carcinoma, 9 died within 18 months. One is still alive, despite numerous recurrences during the past 11 years. Sarcoma of the thyroid gland in four patients was uniformly fatal in a short time.

Vagotomy and Gastroenterostomy in the Surgical Treatment of Duodenal Ulcer. K. R. Trueman and D. L. Kippen. Canad. M. A. J. 75:547-550 (Oct. 1) 1956 [Toronto, Canada].

Twenty-five women and 80 men between the ages of 22 and 78 years with intractable or complicated duodenal ulcer underwent vagotomy and posterior gastroenterostomy at the Winnipeg Clinic in Canada, between May, 1946, and December, 1953. Symptoms had been present for an average of 12 years. Intractable pain was present in 101 patients; it was accompanied by hemorrhage in 41, perforation in 18, and pyloric obstruction in 15. Ninety-three patients were followed up for from 3 to 10 years. Control of the peptic ulcer by vagotomy and gastroenterostomy was good in 77 patients (82.8%) and fair in 6 (6.4%). Results were poor in 10 patients (10.7%). Recurrence of chronic peptic ulceration was demonstrated in only three patients. Moderate hemorrhage without symptomatic or radiological evidence of chronic peptic ulcer accounted for 3 of the 10 poor results. Although postoperative gastrointestinal disturbances of some degree occurred in 11 patients, they were considered to be undesirable side-effects of the operation in only 5. The other six patients had symptoms referable to an irritable colon, which was present before the operation.

Cancer of Stomach and Gastric Ulcer. J. de M. Grey and L. F. de Moraes. Rev. brasil. cir. 32:91-100 (July) 1956 (In Portuguese) (Rio de Janeiro).

Cancer of the stomach coexisting with gastric or duodenal ulcer is far more frequent than is believed. The ulcers are potentially cancerous. They call for surgical treatment whenever the clinical symptoms and roentgen signs persist or reappear after discontinuance of medical treatment and of diet. The period of waiting before resorting to surgery should be no more than five or six months for a duodenal ulcer and three or four months for a gastric ulcer. Three cases are reported. The first patient had resection for a simple gastric ulcer. Histopathological examination of the removed specimen showed the aspects of an ulcer with cancer developing at the base of the ulcer. The second patient had a clinical and roentgen diagnosis of antral cancer. During laparotomy for subtotal gastrectomy, enlarged lymph nodes were observed at the lesser curvature and the cardia. A total gastrectomy was performed. Histopathological examination did not reveal cancer in the antral tumor, but the lymph nodes proved to be metastases of mucoid carcinoma. The third patient, a man of 70, complained of gastric symptoms of two years' duration. Roentgen examination showed an antral tumor. During laparotomy for subtotal gastrectomy another tumor was observed. It was larger than the antral tumor and was located on the greater curvature and the cardia. Histopathological examination showed two distinct tumors of the same type, without any involved tissue between them. The authors advise early gastrectomy for gastric and duodenal ulcers that do not respond to diet and medical treatment and also for gastric tumors presenting the roentgen appearance of gastric cancer.

Clinical and Pathophysiological Problems of Total Gastrectomy in Patients with Carcinoma of the Stomach. T.-O. Lindenschmidt. Ztschr. klin. Med. 154:200-215 (No. 2) 1956 (In German) [Berlin, Germany].

Thirty-three men of the average age of 56 years and 17 women of the average age of 62 years with advanced carcinoma of the stomach were operated on at the surgical clinic of the University of Hamburg-Eppendorf, Germany, between 1950 and 1954. Forty patients had total gastrectomy and 10 had subtotal gastrectomy with 1, 2, or 3 cm. of stomach left below the cardia. There were 22 operative deaths. Fifteen patients died within from 3 to 36 months after their discharge from the hospital following the operation. Three patients were lost to follow-up. Ten patients are living with an average survival time of 30 months. The tumors invaded all the parietal layers in all the patients. Metastases were found at the operation in the lymph nodes of 6 of the 15 patients who died after their discharge from the hospital. Of the 10 still living, only one had metastases of the lymph nodes of the omentum, which was removed at the operation.

The author is convinced that indications for surgical treatment of advanced carcinoma of the stomach should be widened. There are no reliable historical, clinical, or roentgenologic data

excluding operability of the tumor. Subtotal or total gastrectomy, with simultaneous removal of all the suspicious lymph nodes and of the metastasized omentum, if necessary, is required if the size of the tumor is such that the resection, either toward the pylorus or toward the cardia, cannot be made at a distance of at least 5 cm. from the tumor. The simultaneous removal of adjacent organs affected by the tumor must be decided on in the course of the intervention. Pathophysiological considerations do not limit subtotal or total gastrectomy, provided that the patient is given adequate substitution therapy in the preoperative and postoperative period. Such therapy should consist of adequate administration of proteins in order to break through the vicious circle between protein deficiency and enzyme deficiency. Pancreas preparations should be supplied to improve the utilization of proteins and fats. Parenteral iron therapy is indicated in the presence of anemia due to iron deficiency. Vitamin B_{12} and folic acid therapy are indicated in the presence of megaloblastic anemia. Vitamin B complex therapy is important for the prevention or treatment of manifestations of vitamin B deficiency after total gastrectomy, such as glossitis, pharyngitis, cheilitis, and esophagitis. Total gastrectomy is not indicated in patients in whom all the adjacent organs, i.e., liver, pancreas, spleen, diaphragm, mesocolon, and colon, have become infiltrated by the carcinoma, requiring such a formidable intervention that only exceptional patients may survive. In addition, the prognosis is not favorable as regards freedom from relapses and metastases in patients with involvement of suprapancreatic and para-aortal lymph nodes, and it is particularly unfavorable in patients in whom the tumor has invaded all of the parietal layers.

Primary Resection of Stomach in Free Perforation of Gastroduodenal Ulcers. R. Baltzersen. Nord. med. 58:1195-1196 (Aug. 23) 1956 (In Norwegian) [Stockholm, Sweden].

In Haukeland Hospital in Bergen 179 cases of free perforation of gastroduodenal ulcers (134 cases of perforated duodenal ulcer, 45 of perforated gastric ulcer) were treated from 1942 to April, 1955, with a total mortality of 9.5%. Primary resection of the stomach according to Billroth 2 or its modifications was done in 118 of the cases, with 5 deaths, all in men with duodenal ulcers. From 1938 to April, 1955, a total of 313 gastroduodenal perforations into the free peritoneal cavity were treated with 32 deaths or a mortalityy of 10.2% Of the 175 patients in whom primary gastric resection was performed, 7, or 4%, died; they were all treated for perforated duodenal ulcer. Only one death occurred in the 67 primary resections performed after 1947, giving an operative mortality of 1.5%. In the 605 gastric resections performed in the same period for nonperforating ulcers the mortality was 1.2%.

Experiences with the Treatment of Acutely Massively Bleeding Peptic Ulcer by Blood Replacement and Gastric Resection. J. D. Stewart, J. H. Cosgriff and J. G. Gray. Surg. Gynec. & Obst. 103: 409-415 (Oct.) 1956 [Chicago].

Immediate blood replacement and early gastric resection has been used by Stewart and associates since January, 1947, in the treatment of patients with massively bleeding peptic ulcer. They review observations on 193 patients on whom 196 operations were performed. Chronic duodenal ulcer, penetrating in nature, was the commonest lesion, while chronic gastric ulcer was second in frequency. Shallow ulcer associated with a brief or nondescript history of ulcer dyspepsia was not uncommon, accounting for approximately 20% of the gastric lesions. In 21 patients the site of bleeding was not satisfactorily determined at operation. During the series of 196 operations on 193 patients, 22 patients were found to have other causes for bleeding. There were 13 malignant lesions of the stomach and 4 of the duodenum and pancreas. Of the 3 patients with hemorrhage from esophageal varices, one had extrahepatic portal bed block, or Banti's syndrome. The appropriate operation was carried out when the true diagnosis became evident in these 22 patients, and at least one of those who had gastric resection for hemorrhagic gastric carcinoma under these circumstances is alive and well over five years later. Subtotal gastrectomy was performed in 186 of the patients.

Twenty-five of the patients died. There were two deaths among the 65 patients less than 50 years old (3%) and 23 (18%) among the 128 patients over 50 years of age. Half of the patients who recovered and three-quarters of those who died had serious associated diseases. There was a high incidence of cardiovascular disease in patients over 50 years of age. The commonest postoperative complications in patients who recovered were wound infection and dehiscence, pulmonary atelectasis, and pneumonia; commonest in those dying were cardiac complications. Dehiscence of the duodenal stump, stomal arrest, transfusion reaction, and postoperative hemorrhage were rare. The average amount of blood given before and during operation was 2,600 cc.

The Management of Ascites with Radioactive Gold. R. J. Ireton and J. C. Ullery. Surg. Gynec. & Obst. 103:437-442 (Oct.) 1956 [Chicago].

Radioactive colloidal gold (Au^{198}) has been used in the treatment of ascites at the Ohio University Hospital since 1952. The group treated included 35 patients with proved ascites secondary to tumor. Three of these patients received a second Au^{198} treatment, for a total of 38 treatments. There were 3 men and 32 women with an average age of 55 years, the youngest 29 and the oldest 75 years old. The type of tumor varied, but the majority were some type of adenocarcinoma. Two-thirds of the adenocarcinomas were primary in the ovary. The patients were divided into 3 groups. Group 1 is composed of patients with no evidence of reaccumulation of ascites at the time of follow-up or death. There were nine patients in this group, five of whom are still living after from 2.5 to 17 months. Group 2 consists of patients who had a remission of ascites for at least six weeks. There were seven patients in this group, four of whom are still living after from two to six months. Group 3 consists of those patients in whom there was no remission or only transient remission of ascites. There were 19 patients in this group. Nine of these patients expired within six weeks of treatment and only two are still living, for five and nine months respectively.

Factors that might explain the differences in the results are reviewed, with the following conclusions: 1. The type of tumor was of some importance, since none of the patients with sarcomas had remissions. 2. That the smaller metastasis was associated with better results was only indicated, not proved. 3. Treatment prior to Au^{198} therapy, treatment after Au^{198} therapy, or combination of the two, whether surgery, radiation, or both, was of little significance in the remission of ascites. 4. The general condition of the patient was important, since one-half of the patients experiencing no remission died soon after treatment. One-half of the patients with pain obtained relief. Complications solely attributable to Au^{198} were uncommon and minor. The authors make a plea for the earlier use of Au^{198}, suggesting that it should be used prophylactically.

A Clinicopathologic Study of the Epiploic Appendages. T. E. Lynn and J. M. Waugh. Surg. Gynec. & Obst. 103:423-433 (Oct.) 1956 [Chicago].

This inquiry into the conditions produced by disease of the epiploic appendages is based on literature reports and on a detailed review of the clinical, surgical, and pathological data in 17 patients observed at the Mayo Clinic from 1940 to 1953. The available literature revealed reports of 158 cases of symptomatic pathological changes of the epiploic appendages prompting surgical intervention. Inflammation (appendagitis) was present in 109 of these cases, intestinal obstruction had been produced by the appendage in 13, and in 34 the appendages were intrahernial. There was primary intra-abdominal appendageal disease in 12 of the 17 patients treated at the Mayo Clinic and in two of these the presenting picture was that of intestinal ob-

struction. Intrahernial epiploic appendagitis occurred once. In the remaining four patients, other disease processes caused the major symptoms or incited the pathological changes in the appendages. During the same period 129 instances of diseased epiploic appendages without symptoms were found; the majority of these appendages had become detached and were found as intraperitoneal loose bodies.

Pathological changes in epiploic appendages may mimic many acute abdominal inflammatory syndromes; they may form an intra-abdominal mass or produce mechanical intestinal obstruction. They may also be a source of pain in a hernia or may be the sole occupant of an incarcerated hernia. Detached epiploic appendages are the most frequent cause of intraperitoneal loose bodies. These may become secondarily attached elsewhere in the abdomen and be confused with a neoplastic process. Infarction of epiploic tags with superimposed epiploic appendagitis has usually been confused clinically with acute vermiform appendicitis. A preoperative distinction can only be tentative. Should laparotomy fail to disclose the usual sources of acute abdominal pain, epiploic appendagitis deserves consideration. An inflamed epiploic appendage may occasionally produce chronic or recurrent symptoms. The treatment is surgical excision of the diseased appendage. Rarely, a diverticulum of the colon will be encountered within the appendage.

Problem of Intrahepatic Cholangitis Accompanying Cholelithiasis. T. Burckhart. Chirurg **27**:408-412 (Sept.) 1956 (In German) [Berlin, Germany].

Eighty-six women and 26 men, 68 of whom were between the ages of 41 and 60 years, underwent cholecystectomy at the surgical clinic of the University of Mainz, Germany, because of a definite clinical suggestion of lithiasis. A preoperative diagnosis of cholangitis had not been made in any of the 112 patients. Biliary calculi were present in the gallbladder in 102 patients and in the common bile duct in 10. Chronic cholecystitis was observed in 93 patients, and only 5 were without abnormal changes in the wall of the gallbladder. A biopsy specimen was obtained from the liver in all patients in the course of the cholecystectomy. Intrahepatic cholangitis was found in 37 patients; other changes in the liver, including pronounced lymphocyte infiltration of Glisson's capsule, increased interstitial connective tissue, diffuse or central fatty degeneration, biliary cirrhosis, and brown atrophy, were present in 36 patients. Fifty-one patients had a history of icterus or were jaundiced at the time of the operation. Nine of the 11 patients between the ages of 61 and 76 years had abnormal changes in the liver, but none of the 33 patients between the ages of 17 and 40 years had such changes. The incidence of cholangitis increases with advancing age. The duration of the cholelithiasis was less than one year in 49 patients, 35 of whom had cholangitis. One-half of the patients with cholangitis also had icterus.

These findings suggest that the presence of a clinically more or less silent intrahepatic cholangitis must be considered as an accompanying disease in patients with apparently uncomplicated cholelithiasis and cholecystitis. Appropriate preoperative treatment should be instituted. Removal of a small biopsy specimen, which in the author's patients was performed without any damage or complication, is justified. The incidence of residual or postoperative complaints after cholecystectomy will thus be reduced and severe early and late complications prevented.

Outcome of Surgery for Ulcerative Colitis. B. N. Brooke. Lancet **2**:532-536 (Sept. 15) 1956 [London, England].

What is the expectation of life of patients who have had total colectomy for ulcerative colitis? To find an answer to this question Brooke reviewed the records of the 131 patients with ulcerative colitis who had been operated on by him. In five patients only emergency or diagnostic laparotomy was undertaken; 126 underwent elective surgery (117 excision and permanent ileostomy and 9 resection and anastomosis). The group included 84 females and 47 males. The youngest patient operated on was 6 years old, the colitis having started two years earlier. Operation was resorted to when the patient's general condition had continued to deteriorate despite conservative measures; when the patient was otherwise unlikely to return to normal life; for complications, both anorectal and remote; for the acute emergencies of hemorrhage and perforation; for carcinoma; or to remove this potential hazard in late cases.

There were 15 operative and late deaths. This represents a mortality of 12%—about half the mortality of the disease treated conservatively in the precortisone era. The majority of late complications of operation arose in connection with the ileostomy. Eversion suture of the mucosa to the skin is advocated to reduce the incidence of stenosis. Revision of the ileostomy was required in some cases to enable the patient to use an adherent ileostomy bag. A follow-up extending to five years and longer in over a third of the survivors indicates that ileostomy should no longer be dreaded as an impediment to full, normal life; indeed, it restores patients with ulcerative colitis to full work, full weight, and an enjoyment of ordinary pastimes. In about half the patients the diet has to be restricted slightly. Patients regard their ileostomies as satisfactory. Resection and anastomosis with preservation of the anal sphincter (9 cases) has been less satisfactory in this series than excision and permanent ileostomy (117 cases). The disease may recur after sphincter-saving resection, and its complications may then arise for the first time. This method is not recommended as a routine, and its indications are limited; it is precluded for rectal hemorrhage and perforation.

Inguinal Hernia in Female Infants and Children. C. T. Kristiansen and W. H. Snyder Jr. West. J. Surg. **64**:481-484 (Sept.) 1956 [Portland, Ore.].

Incarcerations in inguinal hernias are frequent in both male and female infants and frequently require emergency surgery. Kristiansen and Snyder of the California Children's Hospital made a study of incarcerations in the female infants who had received treatment at their hospital from January, 1946, through January, 1955. Of a total of 3,142 inguinal hernias, 351 occurred in girls. One hundred four of the 2,791 hernias in boys were incarcerated or strangulated (3.7%), whereas 51 (15%) of the 351 inguinal hernias in girls were incarcerated or strangulated. One hundred sixty or 45% of the hernias in female infants occurred in the group aged one year or under, and this age group contained all of the incarcerated hernias in female infants and children. After the first year of life the incidence of hernias is fairly constant for each year, with no incarcerations or strangulations. Ovary only, ovary and tube, or ovary and small intestine were found in the hernial sac of all but 3 of the 51 female infants with incarcerated inguinal hernia. The ovary and tube were swollen with some discoloration in almost every instance, indicating that prolonged delay may result in some permanent damage to the ovary and its follicles. Tissue death was observed in only one of the infants and even here the ovary was not removed. The authors believe that the surgeon can rely on the recuperative powers of the ovary. The organ should not be removed, but should be replaced in the abdomen. Infants and children tolerate surgical repair of a hernia very well, and since there is a negligible mortality, surgical treatment should be carried out as soon as a hernia is discovered. In view of the fact also that the incidence of incarceration is highest in the first year of life, the age of the infant should be no deterrent to operative intervention. This is especially true in female infants, as in this study incarceration occurred five times as frequently in the females as in the males.

Giant Cell Tumor of Tendon Sheath. F. L. Flack. J. Oklahoma M. A. **49**: 339-340 (Sept.) 1956 [Oklahoma City].

The patient was a 48-year-old woman who had had some pain and swelling of her hand for 10 years but who had continued her employment as a maid in a hotel until shortly before admission to the hospital, when she caught her hand in a clothes wringer. This forced her to seek help because of greatly increased pain.

There was a tumor mass measuring 20 by 15 cm. involving the entire left hand. The fingers seemed to stick out of the mass. There were many ulcerations, some of them 3 to 4 cm. in diameter. The whole mass was hot, red, tender, and foul smelling. An x-ray film of the hand showed erosions of the cortices of the metacarpals and phalanges with dislocations of some of the joints. Two days after admission she was given 500 ml. of whole blood, but a day later her hematocrit was only 16. She received 500 ml. of whole blood daily for the next five days, and on the ninth hospital day, the patient having received 7 million units of penicillin over this period, the arm was amputated just above the elbow. She was ambulant the next day and was discharged from the hospital on the 12th postoperative day with all of the incisions well healed.

The tumor on microscopic examination proved to be a giant-cell tumor of the tendon sheath. In some sections there were multiple nodules with many foam cells. In others there were nodules composed of giant cells. All through this nodular tumor were acute and chronic inflammatory cellular elements. The foam cells seem to be of special significance, since they are rarely seen in malignant tumors thought to arise from periarticular structures but are a characteristic feature of the benign lesions arising in the same structures. A giant-cell tumor of a tendon sheath reaching a size like that of the tumor described is a very rare finding.

Pathological Fractures: Treatment by Internal Fixation and Irradiation. M. B. Devas, J. W. Dickson and A. M. Jelliffe. Lancet 2:484-487 (Sept. 8) 1956 [London, England].

The results of internal fixation in a series of 18 pathological fractures are described. The operation should be done early, since any delay will increase the difficulty of resetting the displaced fragments. Postoperative swelling is the rule, but pain is not severe and can be controlled by analgesics. The method of internal fixation will vary with the site of the fracture. In the present series, seven malignant and one nonmalignant pathological fracture of the shaft of the femur have been stabilized with a Küntscher nail. Six fractures due to metastases and one due to a nonmalignant lesion of the femoral neck and intertrochanteric region have been stabilized with a Smith-Petersen pin or with a nail and plate. Three pathological fractures of the shaft of the humerus due to metastasis have been treated by the insertion of a Rush pin.

The techniques for the internal fixation of pathological fractures are identical with those for the internal fixation of nonpathological fractures, and the same attention must be paid to gentle handling of the tissues, accurate placing of the chosen device, and absolute asepsis. An antibiotic cover is advisable if there is any doubt as to the complete sterility of the procedure. Closed reduction of the fracture is the safest method, but open reduction may be needed because of malignant infiltration at the fracture site. The results of internal fixation in this small series have been satisfactory. All patients experienced considerable or complete relief of pain, and some patients with widespread malignant disease were able to resume an active life. Postoperative pain was easily controlled, and no patient died as a result of the procedure. The authors believe that all pathological fractures of the long bones should be considered for operation. Prophylactic internal fixation is indicated where there is a real risk of fracture.

NEUROLOGY & PSYCHIATRY

Penicillin Treatment of Asymptomatic Central Nervous System Syphilis: I. Probability of Progression to Symptomatic Neurosyphilis. R. D. Hahn, J. C. Cutler, A. C. Curtis and others. A. M. A. Arch. Dermat. 74:355-366 (Oct.) 1956 [Chicago].

Of a total of 765 patients with asymptomatic syphilis of the central nervous system who were treated with penicillin at eight different hospitals, 34 (4.4%) were given less than 2,400,000 units as the total dose of the antibiotic, 163 (21.3%) were given total doses of penicillin varying between 2,400,000 and 4,799,999 units, 258 (33.7%) were given total doses varying from 4,800,000 to 8,999,999 units, 306 (40%) were given 9 million units or more, and in 4 (0.5%) the amount of drug given was unknown. Two hundred sixty-four patients had not received previous treatment, and whatever previous treatment the other 501 patients had been given was inadequate to produce a cure. The 765 patients were followed up after the penicillin treatment for periods ranging up to six or seven years. The maximum cumulative probability of clinical progression from asymptomatic to symptomatic neurosyphilis was calculated in these patients as 0.55% at the first year, 1.69% at the third year, 2.02% at the fifth year, and 3.31% at the seventh year after the treatment for syphilis. Only 12 of 765 treated patients were recorded as having shown progression of asymptomatic neurosyphilis at the last observation period. Of these patients, only one was unequivocally a treatment failure; this patient responded satisfactorily to retreatment with a larger dose of penicillin. In the other patients there was no clear-cut evidence that the so-called progression did in fact represent progress of the disease process.

In this group, progression could not be related to any of the factors, such as age, race, sex, previous treatment, and retreatment status, considered in the analysis, except in a single patient in whom lack of cooperation precluded treatment when spinal fluid examination clearly indicated a relapse requiring retreatment. Progression, with but one exception, consisted of what can be considered minor neurological or psychiatric changes, and none of the patients was incapacitated by the so-called progression. It is probable that what is considered as progression represents manifestation at the level of clinical recognition of pre-existing subclinical neuraxis damage. The authors' observations suggest that asymptomatic syphilis of the central nervous system responds extremely well to treatment with penicillin; within the study period of from six to seven years it appears that penicillin alone is capable of completely curing asymptomatic syphilis of the central nervous system.

Penicillin Treatment of Asymptomatic Central Nervous System Syphilis: II. Results of Therapy as Measured by Laboratory Findings. R. D. Hahn, J. C. Cutler, A. C. Curtis and others. A. M. A. Arch. Dermat. 74:367-377 (Oct.) 1956 [Chicago].

This report deals with the pretreatment and post-treatment status in terms of results of blood and spinal fluid examinations of the 765 patients with asymptomatic syphilis of the central nervous system who were treated with penicillin and were evaluated in the preceding paper with regard to the probability of progression to symptomatic syphilis. Changes in results of laboratory tests after treatment with penicillin were related to the test status of the given patient in a given clinic at the time of the study treatment with penicillin. Test results were considered to be essentially unchanged, less positive, or more positive. In this way changes in laboratory findings from the eight hospitals in which the patients were treated were analyzed as in a single group of patients. The range of cell count in the cerebrospinal fluid of from 5 to 10 and total protein of from 40 to 50 mg. per 100 cc. was to be considered a borderline zone and was probably within the limits of normality. After successful treatment with penicillin, abnormal cell counts disappeared almost completely within four years; total protein values changed more slowly and did not show the same degree of reversion to what were considered normal limits within that period.

As measured by the fall in cell count, which is the most sensitive index, no clear-cut relationship between success or failure of treatment and size of penicillin dosage could be demonstrated. At most, from cell count studies, it would seem that 9% of the patients might be expected to show a need for retreatment at the end of one year's observation, without regard to the original penicillin dose used. This probably represents a composite group of patients who are failures and patients slow to respond.

It appears that persistently abnormal spinal fluid total protein levels are not, in themselves, indicative of poor prognosis. Significant differences in total protein response were observed in relation to sex and race. The total protein outcome was less favorable in white persons than in Negroes and in men than in women. Spinal fluid tests for syphilis showed a gradual decrease in positivity with the passage of time after treatment; this was more pronounced in the group receiving only a single course of penicillin. Improvement in the spinal fluid test for syphilis was more rapid in the younger patients, in those with disease of shorter duration, and in those with abnormal cell count. A minimum of 28% of the patients with asymptomatic neurosyphilis had a blood serologic titer of 2 units or less. Thus, a weak serologic reaction cannot be considered as indicating absence of spinal fluid involvement. After penicillin treatment of asymptomatic syphilis of the central nervous system there was a gradual trend toward seroreversal, with some patients having more strongly postive results from the serologic test or having positive results after previous negativity. There seemed to be no relationship between serologic negativity and degree of spinal fluid positivity at the onset of the study treatment with penicillin. Changes in the blood serologic test for syphilis after penicilin treatment did not reflect, with any degree of accuracy, changes in the spinal fluid test for syphilis.

Asymptomatic syphilis of the central nervous system responded extremely well to treatment with penicillin. Retreatment on the basis of persistent positive laboratory findings alone is not recommended unless the cell count increases significantly after treatment, remains unchanged at an elevated level for six months after treatment, or increases significantly after approaching normalcy or near-normalcy after treatment.

GYNECOLOGY & OBSTETRICS

Variables in the Diagnosis and Management of Vulvar Carcinoma as Observed by the Philadelphia Committee for the Study of Pelvic Cancer. G. A. Hahn. Am. J. Obst. & Gynec. **72:** 756-770 (Oct.) 1956 [St. Louis].

The 131 women with vulvar carcinoma reviewed were treated in 20 different Philadelphia hospitals. The patients were almost equally divided between parous and nulliparous women. Ninety-nine of the women had ceased having menstrual periods, the menopause having been artificial in 11 of them. The most common symptoms causing the patient to seek medical advice were, in the order of their frequency, pruritus, a lump, bleeding, dysuria, pain, ulcer, and discharge. Diabetes mellitus existed in eight of the patients, and six had primary carcinoma elsewhere: two in the breast, one in the buttock, and three in the genital organs (endometrium, ovary, and cervix). The breast and cervical cancers had been diagnosed before, and the carcinomas of the buttock, ovary, and endometrium were discovered at the time the vulvar lesion was being studied.

Delay on the part of the patient alone was a contributing factor in the failure to obtain adequate treatment in 45 instances. In 42 additional patients, physicians or institutions or both had caused further delay, that is, "patient delay" was a factor in 87 (66.41%) of the women. The average delay in seeking a physician's advice was 2.35 years and the longest delay was 12 years. Hope that the difficulties would disappear with time, fear of cancer or that some surgical procedure might be necessary, being too busy, absence of pain, or being too old for any type of surgery were reasons given for not consulting a physician. Only once was finances given as the reason for not asking for a physician's help.

There were 24 women (18.31%) in whom physicians were considered to be wholly to blame for delaying the diagnosis of vulvar malignancy. Three times an institution was considered to be at fault, and in five cases an institution was considered to have contributed to delay. More than one physician was responsible for delay in 12 instances. One patient had visited five physicians before an adequate diagnosis was made. One patient had been hospitalized in two different institutions for orthopedic treatment and had also been under the care of a private physician. The final step in her diagnosis was made by a registered nurse who noted the vulvar growth during her care of the hospitalized patient. In most cases failure to examine the patient was the cause for the delay in making a proper diagnosis. Improper diagnosis was the next most common cause of physician delay. Sixteen different types of treatment, or treatment combinations, were employed in the 127 patients who were treated. Radical vulvectomy with node dissection was most frequently used, then radical vulvectomy alone, and finally x-ray therapy. Fifty-seven patients observed five or more years had a survival rate of 47.37%. The patients who had been treated by radical vulvectomy and bilateral groin dissection had a five-year survival rate of 78.94%. The author believes that the most important factor bringing about a favorable five-year survival rate is the type of therapy rather than the delay involved.

Value and Risk of Pertubal Insufflation. P. Lange. Acta Obst. et gynec. scandinav. **35:** 354-365 (No. 3) 1956 (In English) [Stockholm, Sweden].

Two hundred ninety-one women were subjected to 342 kymographic uterotubal insufflations at the fertility department of the Municipal Hospital of Copenhagen, Denmark, between Jan. 31, 1951, and Dec. 31, 1952. Uterotubal insufflation revealed tubal nonpatency in 110 of the 291 patients. Hysterosalpingography was performed after several weeks or months in 83 of the 110 patients. Tubal nonpatency was confirmed by hysterosalpingography in 46 of the 83 patients. Hysterosalpingography showed a normal tubal picture in 23 patients, i.e., there was definite disagreement between the results of tubal insufflation and hysterosalpingography. Hysterosalpingography showed definite abnormal changes in the remaining 14 patients, but there was evidence of peritoneal spill suggesting a certain degree of patency. "Relative" disagreement between the results of tubal insufflation and hysterosalpingography was suggested in these patients. Thus complete agreement between the results of the two methods was found in 55.4% of the patients, definite disagreement in 27.7%, and relative disagreement in 16.9%.

Tubal patency was revealed by the first or subsequent enterotubal insufflation in 181 patients. One hundred eleven of these patients presented a normal kymographic curve; hysterosalpingography was performed in 38 of these 111 patients, and the results were normal in 30. The remaining 70 patients had an abnormal kymographic curve; hysterosalpingography was performed in 33 of these and revealed unquestionable nonpatency in 6 and various forms of anatomic abnormality in 27. The incidence of complications of uterotubal insufflation was surprisingly high with definite pelvic inflammations occurring in 11 patients, i.e., in 3% of the 342 insufflations. No death resulted from uterotubal insufflation, and only two of the 11 patients required admission to hospital, the other 9 being treated as outpatients. None of them required surgical treatment.

The therapeutic effect of uterotubal insufflation was small in that 22 of the 291 patients conceived and only 4 of these fulfilled all the criteria relating the conception to the uterotubal insufflation. The author's observations suggest that a normal kymographic tracing gives considerable certainty of tubal patency. Yet in about 5% of the patients with a normal kymographic curve hysterosalpingography revealed nonpatency. When nonpatency is ascertained by uterotubal insufflation, the examination should be repeated or hysterosalpingography performed.

A Consideration of the Problems of Radiosensitivity in Cancer of the Cervix. S. B. Gusberg. Am. J. Obst. & Gynec. **72:** 804-819 (Oct.) 1956 [St. Louis].

Gusberg outlines the three principal methods for radiosensitivity testing of cervical cancer that have been used in recent years to supplement clinical analysis: histological and cytochem-

ical methods have been used to measure the tumor response, and cytological methods have been used to measure the host response. The histological changes have been codified by Glucksmann, who claims that tumors of high differentiation are more radiocurable than those that are anaplastic. Radiosensitivity and radiocurability may not be identical concepts. The second type of investigation is cytological and concerned with host response. The thesis was developed that the radiation response of normal vaginal cells was more important than the response of tumor cells. Recent work is concerned with material obtained before treatment and with sensitization response. It is believed that, if a patient with a cervical cancer has in her vaginal smear 10% or more of benign vaginal cells with a certain quality, she will respond favorably to radiation, whereas if she has less than 10% she will respond poorly to radiation but will have an excellent result if treated surgically. Sensitization response supposedly measures an immune response by the host.

The third type of radiosensitivity investigation is that current in the author's own laboratory. It rests on the thesis that cancer cells dying under radiation will have an alteration in their nucleic acid pattern. Cytochemists have demonstrated that there are two general types of tumor cells, so-called A cells, which are viable and aggressive and have a heavy chromatin pattern (an important site of desoxyribonucleic acid [DNA]) and relatively obscure nucleoli; and B cells, which are relatively inactive, devitalized, perhaps prenecrotic tumor cells whose chromatin pattern is becoming more obscure and therefore have a relatively lowered nuclear content of DNA but whose nucleoli are very prominent, and thus have a relatively higher ribonucleic acid (RNA) configuration in their nuclei. Studies were begun on the basis of the thesis that the growing edge of a cervical cancer prior to radiation should be rich in A cells, and that this zone might show a conversion to a predominance of B cells under radiation if it were responding properly by healing. Four quadrant biopsies were obtained from the growing active zone of the tumor before, and at weekly intervals during, radiation. It was found that healing of cervical cancer in the human can be predicted with some uniformity from the observation of nuclear changes occurring within three weeks after the beginning of radiation in the growing, vital zone of the tumor. The observed changes include: (1) enlargement of the cell and its nucleus; (2) a relative diminution in DNA evidenced by a sort of dilution of the chromatin masses; and (3) a relative increase in DNA as evidenced by an increase in nucleolar size and number. It has been possible to predict tumor healing if there is a shift away from a predominance of an A cell, or active phase, in the growing zone, toward a B cell, or regressive phase. This change implies an alteration in the DNA/RNA ratio with a relative shift toward RNA predominance. The methods as yet are not precise, and these changes are relative: the RNA seems to increase at about the same rate as does the general cell and nuclear volume; the DNA, on the other hand, probably changes very little and therefore shows a relative decrease in concentration. This suggests a specific effect of irradiation on the synthesis of DNA. The author hopes that studies of nucleoprotein patterns will make it possible to predict tumor-cell death in a uniform fashion before conventional histological or clinical methods can detect it. Such cytochemical prognostication could indicate continuation of radiation for those with good response, supplementary lymph node dissection for those with fair response, and discontinuation of radiation in favor of radical hysterectomy for those with poor response.

Subarachnoid Hemorrhage and Pregnancy. D. E. Cannell and E. H. Botterell. Am. J. Obst. & Gynec. 72: 844-853 (Oct.) 1956 [St. Louis].

The authors report 16 women in whom subarachnoid hemorrhage occurred during pregnancy and who were admitted to the obstetric and neurosurgical services of the Toronto General Hospital from Jan. 1, 1950, to Dec. 31, 1955. In four patients subarachnoid hemorrhage occurred with other complications of pregnancy; three of them died. Of the two patients with preeclampsia, one died after cesarean section and the other recovered. The third patient died as a result of thrombosis of the superior sagittal sinus 32 days after an apparently normal pregnancy and delivery. The fourth patient died of subarachnoid hemorrhage from a mycotic aneurysm of the basilar artery following subacute bacterial endocarditis and septicemia after a septic abortion. The remaining 12 patients experienced subarachnoid hemorrhage in otherwise normal pregnancies. Twenty episodes or recurrences of subarachnoid hemorrhage occurred in these 12 patients. Thirteen were primary, and 7 were recurrences shortly after the initial hemorrhage. One patient had subarachnoid hemorrhage in two different pregnancies. Of 13 major primary subarachnoid hemorrhages, seven occurred in the first 20 weeks of pregnancy, four in the latter 20 weeks, and two in the puerperium. None occurred during labor, though the effects of labor as a precipitating factor cannot be discounted in the two that occurred early in the postpartum period. Six of the subarachnoid hemorrhages arose from intracranial aneurysms, three from arteriovenous malformations, and in three the source of bleeding was undetermined. Subsequent angiograms or autopsies show that aneurysms are the cause of a significant number of the subarachnoid hemorrhages said to be of "undetermined origin."

Regarding the diagnosis the authors say that severe headache, often occipital in distribution, nuchal rigidity, nausea and vomiting, loss of consciousness, hemiplegia, and involvement of cranial nerves occurred in this order of frequency. Auscultation of the skull, and particularly the eyeballs, may demonstrate a bruit, diagnostic of arteriovenous malformation. The clinical diagnosis was confirmed by the withdrawal of grossly bloody spinal fluid under pressure. Clinical neurological examination, alone, frequently fails to localize the site of the bleeding. Cerebral angiography is an indispensable step in the diagnosis. Prompt surgical treatment is indicated in pregnant patients in whom subarachnoid hemorrhage occurs as the result of a ruptured berry aneurysm or arteriovenous malformation. The obstetric management of such patients should be based upon sound obstetric principles, cesarean section being employed on indication rather than election.

ACTH and Hyperemesis Gravidarum. E. Ferrario. Minerva ginec. 8: 586-590 (July 31) 1956 (In Italian) [Turin, Italy].

The author studied the effect of corticotropin on the urinary excretion of corticoids and 17-ketosteroids in normal pregnant women and pregnant women with hyperemesis. Four patients affected with severe forms of hyperemesis were given corticotropin. Previous treatments had had no effect on these patients. The results obtained with corticotropin were very good. They seem to prove that adrenal hypofunction of adrenocortical and hypophysial origin is involved in the hyperemesis gravidarum syndrome. The dosage and administration of the hormone cannot be standardized. In general, when the administration of ACTH is stopped the symptoms reappear and readministration of ACTH is required. The authors had no side-effects with the product that they used. If the dosage is not high, the danger to the fetus is limited. Undesirable effects of the drug are dependent on the species of the animal, the dosage, and the stage of pregnancy in which corticotropin treatment is started. A very low dosage does not involve any risk. ACTH does not seem to pass the placental barrier. The possible damage to the adrenal glands of the fetus seems to be caused by the transplacental passage of excessive corticoids produced by the mother. Hyperemesis gravidarum runs its course in three well-differentiated stages: a psychogenic stage, an intermediate stage, and a stage characterized by a true gravidic toxicosis brought about by changes in metabolism caused by liver damage. ACTH would be of no help in the third stage.

PEDIATRICS

Electrolyte Considerations in Exchange Transfusions for Erythroblastosis Fetalis. R. P. Bolande, H. S. Traisman and H. F. Philipsborn Jr. J. Pediat. 49:401-406 (Oct.) 1956 [St. Louis].

The serum electrolytes were studied in 23 erythroblastotic infants before and after 26 exchange transfusions. Refrigerated blood used to replace the circulating blood of erythroblastotic infants is in many instances hyperkalemic and commonly hypocalcemic (citration effect). Under such circumstances striking alterations in the serum electrolytes of the transfused infants must be anticipated. Particular attention was paid to potassium. Many of the infants received donor blood that was markedly hyperkalemic. The majority of infants tolerated an abnormal load of infused potassium without ontoward physiological effects or significant change in their serum potassium concentrations. In some instances, rapid infusion of hyperkalemic donor blood appeared to be related to cardiac arrest, death, or both. Critical values could not be definitely established from the limited data at hand. Since it is known that the potassium concentration of donor blood is progressively increased during cold storage, the safest procedures would be to use fresh, warm donor blood at a tolerable rate.

Treatment of Erythroblastosis Fetalis with Special Reference to Sensitization to Rh-Hr Factors Other than Rh$_o$. A. S. Wiener, I. B. Wexler and G. J. Brancato. J. Pediat. 49:381-393 (Oct.) 1956 [St. Louis].

A number of modifications in the exchange transfusion technique have been introduced by Wiener and associates. To date, 166 babies with erythroblastosis fetalis caused by Rh$_o$ sensitization have been treated by their latest modification of exchange transfusion by the radial artery–saphenous vein technique. In this latest modification, partially concentrated blood (hematocrit 0.5), preferably not more than three days old, is used. This is prepared by removing part of the citrated plasma after sedimentation has occurred. Depending on the severity of the disease and the size of the baby, from 450 to 900 ml. of such concentrated blood is used for the transfusion. In severe cases the exchange transfusion is repeated, but in no instance are more than two exchange transfusions deemed necessary. Among the 166 babies treated this way, only five died or had neurological sequelae, a crude mortality rate of only 3 ± 0.9%. On the other hand, among babies treated by earlier modifications, by only simple transfusion, or receiving no treatment at all, the mortality rate ranged from 17 to 21%. The difference in results is even more striking when the severity of the disease is taken into account. Thus, among severely affected babies who received no treatment the mortality rate was 65.5 ± 10.6%; among those receiving simple transfusion therapy the mortality rate was 42.1 ± 7.8%; among those treated by previous methods of exchange transfusion the mortality rate was 19.8 ± 2.6%; while among those treated by the latest modification of exchange transfusion, the mortality rate was only 3.8 ± 1%.

Erythroblastosis fetalis caused by sensitization to Rh-Hr factors other than Rh$_o$ poses an important problem, since the routine antenatal screening test for Rh$_o$ sensitization does not take them into account. Such cases are rare, but they are just as serious as instances of Rh$_o$ sensitization. Thus, among nine cases of erythroblastosis fetalis caused by hr′ sensitization, one baby died before treatment could be instituted. Of the remainder, four were treated by exchange transfusion and recovered, while among the four treated by simple transfusion one died and one of the three who survived had severe neurological sequelae. A simple screening test for Rh$_o$ antibodies consists in testing the patient's serum against ficin-treated cells of types Rh$_1$Rh$_1$, Rh$_o$, and rh respectively. This test should be carried out on all women in labor admitted to the obstetric service and on patients admitted to the surgical or other services who might require blood transfusion. Case histories are presented that illustrate the value of this screening test. In patients with hr′ sensitization the antibodies, even when present in high titer, may react only in tests against enzyme-treated cells and may fail to react in the conglutination and antiglobulin tests. This accounts for puzzling, severe cases of erythroblastosis fetalis in which the direct antiglobulin test for coating of the baby's red blood cells by Rh-Hr antibodies is negative. Certain antibodies, such as anti-F and anti-J, are not detected by the enzyme test, so that the screening test against ficin-treated cells should supplement and not replace the other tests for isosensitization.

Causes of Mongolism. J. Øster. Dan. med. bull. 3:158-164 (Aug.) 1956 (In English) [Copenhagen, Denmark].

An average incidence of mongolism of 1 mongol to approximately every 600 live births, or 0.17%, is reported. In Øster's studies of the cases from the lying-in departments of the Rigshospital from 1923 to 1948, as well as in previously published etiological studies in the literature, the only constant finding has been the older age of the mothers of mongols. No evidence has been found to support the view that mongolism might be hereditary. There is no indication for eugenic precautions in the case of women who have had one mongol child, for the risk of their having another mongol child is not significantly greater than that risk for other women of the same age group. It seems clear that various exogenous maternal factors play a part in the occurrence of mongolism, primarily the more advanced age of the mothers and the depressed reproductive faculty in these women. There is room for intensive continued research on the etiology of mongolism.

Toxoplasmosis as Cause of Mongolism. H. O. Kleine. Ztschr. Geburtsh. u. Gynäk. 147:13-27 (No. 1) 1956 (In German) [Stuttgart, Germany].

Kleine demonstrates on the basis of three cases that mongolism is a special form of connatal toxoplasmosis or at least that it can be caused by toxoplasmosis, because he has observed other cases of mongolism in which the mother had a virus infection during the first three months of pregnancy or cases in which rhesus factor incompatibility played a part. He emphasizes the role of toxoplasmosis and regards it as the most frequent cause. He mentions the following factors as evidence that a toxoplasmogenic embryopathy played a part in the three cases reviewed: 1. The mothers gave strongly positive Sabin-Feldman tests and had roentgenologically demonstrable foci of cerebral calcification as well as pigmentations in the eyegrounds. 2. The infants had nystagmus, strabismus, and encephalitis, and one of the mongoloids had an auricular attachment as an accompanying malformation. The fact that "accompanying defects" are the same in toxoplasmosis and mongolism is further evidence of a causal relation between these two diseases, and such defects aid in establishing the period in intrauterine development during which toxoplasmosis produces the characteristics of mongolism. The damage to the embryo during the "organogenetic" period and the concepts of "embryopathy" versus "fetopathy" are discussed. The first three months of gestation are the period of organogenesis, and it is important that the head and brain develop ahead of the other organs. Intrauterine damage is the more severe, the earlier it develops during the period of gestation. The simultaneous appearance of apparently unconnected defects, for instance the simultaneous occurrence of feeblemindedness and syndactylism or the combination of a defect in the cardiac septum and the absence of the middle phalanx of the fifth finger in mongolism can be explained by damage to centers of organization during the early embryonal period. According to the author's theory, mongolism is an exogenic disturbance in development elicited by a diaplacental infection with toxoplasmosis of an embryo still in the phase of organogenesis, that is, during the first three months of gestation.

The fact that the origin is exogenic and not hereditary is highly important, because it makes prophylaxis possible. Expectant mothers or those likely to conceive should avoid contact with foods or articles that have been contaminated by mice or rats. They should avoid all contact with dogs, cats, rabbits, chickens, ducks, pigeons, sheep, and cows, because these animals are the chief hosts of Toxoplasma. In these animals toxoplasma usually produces intestinal ulcerations, but it may also cause bronchopneumonia and meningitis. This form of prophylaxis is the more important because the therapeutic outlook for mongolism is hopeless.

Malignant Diphtheria. M. Rizzardini and O. Undurraga. Rev. chilena pediat. 27:242-236 (June) 1956 (In Spanish) [Santiago, Chile].

Nineteen children of either sex with malignant diphtheria were observed in a pediatric hospital department for infectious diseases between the years 1946 and 1954. Most of the patients were between the ages of 6 and 12 years. They were hospitalized on the second or third day of the disease. They were acutely ill, with symptoms of acute toxemia, extensive necrotic or hemorrhagic pseudomembranes, purpura, great tumefaction of the neck, and renal and cardiovascular complications. The treatment consisted of the administration of diphtheria antitoxin, in an average total dose of 80,000 units, and of antibiotics. None of the patients survived. Autopsy was performed on 17. The diagnosis of diphtheria was confirmed. In 50% of the cases the membranes invaded the buccopharyngeal cavity, the larynx, the trachea, and, in some cases, the branches of the bronchi. The heart and kidneys were the structures most constantly damaged. Malignant diphtheria can be differentiated from the acute forms of diphtheria. The acute toxemia causes the patient to be greatly excited at certain moments and stuporous at others. The disease, which does not respond to any treatment, such as early administration of large or repeated doses of diphtheria antitoxin, alone or with antibiotics, follows a rapid course, with a mortality of 100%.

A Clinical and Biochemical Study of Galactosaemia: A Possible Explanation of the Nature of the Biochemical Lesion. G. M. Komrower, V. Schwarz, A. Holzel and L. Goldberg. Arch. Dis. Childhood 31:254-264 (Aug.) 1956 [London, England].

The authors report two new cases of galactosemia in children born in 1951 and 1953 respectively. The results of clinical and biochemical investigations and the effect of milk or galactose feeding for 8-or-10-day periods are described, with particular reference to blood glucose and galactose levels, galactose excretion, renal function, and blood and plasma phosphorus levels. Reference is made to the work carried out on certain aspects of erythrocyte metabolism in this disease. The causation of the signs and symptoms of the disease is discussed in the light of the findings reported in this communication. The hypothesis is put forward that the varied manifestations of galactosemia may be attributed to localized accumulation of galactose-1-phosphate within the tissues and that the extent to which such accumulation occurs—and consequently the resulting lesion or impairment of function—is determined by the ratio of local concentration of enzymes concerned with the early stage of galactose metabolism. More than 40 cases of galactosemia have been described in the literature. Galactose has always been implicated as the toxic agent, and the development of hepatomegaly, jaundice, cataract, mental retardation, proteinuria, and, more recently, aminoaciduria, have been attributed to the damaging effect of this sugar on each of the organs concerned.

Free Diets in the Treatment of Diabetic Children. C. C. Forsyth and W. W. Payne. Arch. Dis. Childhood 31:245-253 (Aug.) 1956 [London, England].

The clinic for diabetic children at the Hospital for Sick Children, Great Ormond Street, London, was started in 1926. Initially, strictly weighed diets were used with a carbohydrate content of up to 100 gm. daily. It soon became apparent, however, that many of the children were hungry and that they were not growing well. The food intakes were gradually increased until normal in quantity, and in 1936 free diets were tried for the first time. Concentrated carbohydrates, such as table sugar, jam, chocolate, and sweets, are restricted, but unlimited quantities of plain fare are provided. Cooperation is excellent with regard to the regularity of meals, because the importance of avoiding insulin reactions is soon appreciated, and when the diets are analyzed they are remarkably similar from day to day. Although the diet employed is not truly free, there is a real difference between such a simple diet and a strictly weighed diet.

This paper deals only with patients regularly attending the clinic and those who came for examination in response to a letter and were still on a free diet. The duration of diabetes exceeded 15 years in 41 of the 100 patients, and the others had been diabetic for between one and 15 years. Their ages ranged from 3 to 41 years, and the longest period on a free diet was 18 years. The patients were interviewed and examined, particularly for evidence of retinal degeneration and neurological, renal, or vascular disturbances. Except for short periods of loss of balance due usually to intercurrent infections, all patients remained entirely free from thirst, polyuria, or ketosis. Insulin reactions have been mild and hypoglycemic coma has been very rare. Growth has been satisfactory. The incidence and severity of retinitis increased with the duration of diabetes. A rise in the incidence of retinitis was noted only in patients failing to satisfy the standard of control for more than half of their period of diabetes. Because the over-all results of treatment have been as good as those obtained by clinics employing weighed diets and because of the psychological advantages and the better cooperation achieved, the authors believe that the use of a liberal diet will permit the best control in the greatest number of children.

Gastrointestinal Allergy to Cow's Milk in the Neonatal Period. R. B. Tudor. Journal-Lancet 76: 245-248 (Sept.) 1956 [Minneapolis].

Manifestations of gastrointestinal allergy in children are most commonly due to cow's milk. The first allergic symptoms usually occur from birth to 4 months of age. At this time, the intestine may be sensitive when the skin is not. Skin testing is usually inconclusive. The most common symptoms of gastrointestinal allergy due to cow's milk are colic, vomiting, diarrhea, nasal stuffiness, cough, wheezing, and shock. Unless the child is sensitive to the lactalbumin of cow's milk, goat's milk is not a successful substitute because the casein in cow's milk and goat's milk is identical. Soy bean milk, a weak sensitizing protein, is usually the best milk substitute. The author presents histories of seven infants with symptoms of gastrointestinal allergy due to cow's milk. Most of them improved when soy bean milk was substituted for cow's milk. One required a meat base formula, and another had no further difficulty when goat's milk was substituted for cow's milk.

Idiopathic Hypercalcaemia. W. Kidney. J. Irish M. A. 39:64-67 (Sept.) 1956 [Dublin, Ireland].

Idiopathic hypercalcemia occurs in infancy and early childhood and is associated with an increase in serum calcium and blood urea levels. The chief symptoms are inadequate food intake and vomiting, which result in failure to thrive, wasting, constipation, hypotonia, and lethargy. The child is usually small, undernourished, pale or pink, flabby, and quiet or dull. The age is usually over 4 months and under 2 years at the time of onset. The child may be mistaken for a cretin. The facial characteristics are marked epicanthic folds, overhanging upper lip, wide mouth, large lower lip, low-set ears ("elfin" look), and sometimes squint. Depositions of calcium may occur, particularly in the kidneys, giving rise to persistent infection. Idiopathic hypercalcemia must be differentiated from such conditions as pyelitis, renal rickets, pink disease, Albers-Schönberg disease (osteopetrosis), renal acidosis, and Fanconi's nondiabetic glycosuria.

The author describes observations on 13 children with idiopathic hypercalcemia. Children with the mild form may recover in a few months or years, but in those with the severe form physical and mental retardation, stunting, and deposition of calcium in the lungs, muscles, and kidneys may finally lead to death. There is no specific treatment, but elimination of vitamin D may be tried, because the child may have received excessive doses or may be hypersensitive to normal doses. Reduction of calcium intake by the elimination of cow's milk, which contains four times as much calcium as does human milk, may be desirable. Cortisone or one of its modifications usually produces great improvement, but it is too early to decide whether it will prevent the mental retardation so often found in the chronic form of idiopathic hypercalcemia.

UROLOGY

The Resemblance of Hypertrophy of the Prostate to Congenital Polycystic Disease: Reconstruction of Cystic Lesions of Hypertrophied Prostate in Three Cases. R. F. Norris, V. E. Martens and R. W. O'Gara. J. Urol. 76:276-286 (Sept.) 1956 [Baltimore].

The similarity of the lesions of hypertrophy of the prostate and of polycystic disease of the newborn is described, and the lesions in the prostate are illustrated by means of reconstructions from serial sections in three patients. The first prostate was selected for study because it was considered typical of a man in early middle age. The areas of glandular enlargement were localized and not extensive. In the serial sections studied, none of the enlarged glands were seen to be isolated as cysts. The second prostate was selected because it showed a preponderance of glandular hyperplasia and the third because of a preponderance of fibromuscular hyperplasia. Neither gland was unduly enlarged. Greatly hypertrophied prostates were not chosen for study because it was feared that the first changes in structure might be obscured in advanced stages of the disease. As regards polycystic disease of the newborn, evidence has previously been presented by the senior author (R. F. Norris) and his collaborators to show that the embryologic development and differentiation of polycystic organs progresses while the cystic lesions are being formed. As a consequence of the epithelial cystic proliferation, the ducts or epithelial tubules eventually are pinched off as isolated segments or as dilated cysts. This sequence of changes resembles the phenomenon of normal resorption of the provisional organ, the mesonephros. In the latter instance, segmentation of tubules and isolation of glomeruli as cysts normally precede the resorption of these elements as the mesonephros degenerates. Since the first generations of tubules in the metanephros are also thought to be normally provisional, the authors suggest that segmentation and cystic dilatation of the tubules in polycystic disease of the kidney and of other organs represent an extension of this normal process of resorption to a pathological degree. The epithelial lesions of the hypertrophied prostate characterized by cystic dilatation of ducts and acini and by the isolation of blindly-ending cystic complexes resemble the lesions of congenital polycystic disease.

The objection may be raised that polycystic disease of the newborn differs from hypertrophy of the prostate in the short time required for its development. This difference may be more apparent than real if the rapidity of all embryologic development is taken into consideration. So far as the authors know, neither polycystic disease nor hypertrophy of the prostate has been reproduced experimentally in animals. The cause of each disease, therefore, is obscure. Whether there are etiological factors in common is still unknown, but in the case of hypertrophy of the prostate, the belief persists that imbalance of endocrine secretions is the cause of the disease. Endocrine disturbances during pregnancy, however, have not been extensively investigated as a cause of polycystic disease. The conclusion seems warranted that the similarity of the lesions of hypertrophy of the prostate to those of congenital polycystic disease is important not only because lesions of embryologic development can be mimicked in the organs of adults, but also because the two diseases may have etiological factors in common.

Congenital Renal Aplasia with Calcified Cystic Degeneration: Report of Two Cases and Review of the Literature. B. S. Abehouse. J. Internat. Coll. Surgeons 26:283-296 (Sept.) 1956 [Chicago].

The author has collected 16 cases of extensive calcification of cysts in congenitally aplastic kidneys. He describes two additional cases of this unilateral condition in a 40-year-old woman and a 78-year-old man. Analysis of the literature on congenital renal aplasia with and without cystic degeneration and of the observations made in the two patients with congenital aplastic kidneys containing calcified cysts warrants the following conclusions: 1. There is a definite need for an exact definition of the three important congenital anomalies of renal structure, i. e., agenesis, hypoplasia, and aplasia, to enable the urologist and pathologist to diagnose and classify the cases properly. 2. The distinguishing clinical and pathological features of renal agenesis, hypoplasia, and aplasia permit an accurate differential diagnosis, which may be made with the aid of cystoscopic studies, excretion tests with indigo carmine and phenolsulphonphthalein, and roentgenographic studies, particularly excretory urography and retrograde pyelography.

Renal aplasia is characterized by a total lack of definite renal anatomic form and physiological function in infants and children. In adolescents and adults the aplastic kidney may exhibit marked cystic degeneration, apparently the result of arrested development in the metanephric stage. In one patient total excision of the retroperitoneal mass was carried out. Microscopic sections through the cyst wall showed groups of vestigial tubular structures lined in part by pseudostratified tall cuboidal epithelium. There were also scattered small cysts. The cysts were encased in a dense collagenous fibrous tissue. There were foci of calcium deposition as well as of osseous tissue formation. Renal aplasia associated with cystic degeneration has also been described as multicystic or congenital cystic hypoplasia and not infrequently confused with unilateral polycystic kidney and multiple serous cysts of the kidney. The pathogenic and pathological aspects of calcification, ossification, and cartilage in the walls of the cystic type of aplastic kidney are discussed.

Local Hydrocortisone for Hunner's Ulcer of the Bladder. J. H. Johnston. Brit. M. J. 2:698-699 (Sept. 22) 1956 [London, England].

The patients treated were women aged 63, 68, and 73 years in whom interstitial cystitis with ulceration (Hunner's ulcer) had existed for from two to six years. Treatment by bladder distension with the patient under anesthesia, zinc ionization, and vesical irrigation had formerly been carried out on many occasions. In January, 1956, each was treated by cystoscopic injection of hydrocortisone into the bladder. All have shown marked symptomatic improvement beginning a few days after the injection. The total duration of the remission produced by this therapy is not known, but it is to be expected that, when symptoms recur, further infiltration of the bladder musculature will again be effective. The author learned that Schulte and Reynolds obtained satisfactory results with a similar technique using hydrocortisone and hyaluronidase.

OPHTHALMOLOGY

Report on 104 Cases of Glaucoma Operated upon by Galvano-Cautery Puncture. R. Colley. Brit. J. Ophthal. 40:436-438 (July) 1956 [London, England].

Colley performed the first galvanocautery puncture on July 27, 1950, and since that date all patients with glaucoma of whatever type admitted to his care at the Bath Eye Infirmary for operation have been treated by this procedure. In all, 121 galvanocautery punctures were performed on 104 eyes—100 by the author himself and 21 by an assistant. Fifty-four of the operations were performed in chronic simple glaucoma, 34 in acute or subacute glaucoma, and 33 in secondary glaucoma. Local anesthesia was used in 72 and general anesthesia in 49 operations. The operative technique used was a slight modification of the galvanocautery puncture described by Preziozi in 1924 and in 1950. The results in chronic, simple, acute, and subacute glaucoma appeared to be as successful as those obtained with most other operations. In cases of secondary glaucoma—apart from those due to uveitis—the results were very poor.

Although the number of patients operated upon is insufficient for final conclusions, Colley feels that Preziozi's galvanocautery puncture is worth a more extensive trial. It is very similar to Elliott's trephine operation, but is even easier to perform and takes a shorter time. Other advantages of the galvanocautery puncture are that it can be performed under local anesthesia,

especially in old or ill patients, and that the slow escape of the aqueous when the limbus is pierced makes an intraocular hemorrhage very unlikely.

Water-Drinking and Tonography in the Diagnosis of Glaucoma. B. Becker and R. E. Christensen. A. M. A. Arch. Ophth. 56: 321-326 (Sept.) 1956 [Chicago].

Although characteristic field loss and cupping of the optic nerve head establish the diagnosis of glaucoma, therapeutic efforts in the chronic simple variety of this disease depend upon early detection. Methods available for its diagnosis include tonometry, provocative tests, and tonography. The fact that glaucomatous eyes can demonstrate decreased facility of outflow in the absence of elevated intraocular pressure accounts for their earlier recognition by tonography than by tonometry. When tonography was combined with provocative tests, it was noted that some glaucomatous eyes responded with induced impairment of outflow facility in spite of a failure of this procedure to provoke a rise in intraocular pressure. Thus, tonography before and after water-drinking provided a more sensitive method for the detection of glaucoma than did either alone. A comparison is presented of tonometry, water-drinking, and tonography on 175 normal eyes and 188 eyes with chronic simple (open-angle) glaucoma and loss of visual field. The two groups of eyes could best be separated on the basis of data obtained from tonographic tracings one hour after drinking 1 liter of water.

INDUSTRIAL MEDICINE

An Occupational Agent (N-Butyraldoxime) Causing Reaction to Alcohol. W. Lewis and L. Schwartz. M. Ann. District of Columbia. 25:485-490 (Sept.) 1956 [Washington].

An unpleasant reaction after the ingestion of small amounts of alcohol was noted recently in a large printing company. The agent that is absorbed into the body and "sensitizes" the printers is known as the antioxidant N-butyraldoxime. After such "sensitization" the response to alcohol consisted of a reddish, violescent, nonitching, coalescing, macular rash of the face, neck, and upper trunk; congestion of the conjunctiva and nares; congestion of the mucous membranes of the throat, which caused dyspnea without wheezing; and palpitation. The "reaction" to alcohol caused by N-butyraldoxime is similar to but milder than the Antabuse-alcohol reaction. The blood acetaldehyde level, which is elevated by the absorption of N-butyraldoxime, is further markedly elevated shortly after the ingestion of alcohol, and this causes the unusual "reaction." The effects of exposure to N-butyraldoxime largely disappear in 24 hours. Apparently no permanent damage is done to the body by the new agent. A new "cure for alcoholism" may have been found.

THERAPEUTICS

A Class Experiment on Ganglion Block in Human Subjects. W. D. M. Paton and H. Steinberg. Brit. M. J. 2:622-627 (Sept. 15) 1956 [London, England].

The pharmacology class at University College Hospital in London provided an opportunity whereby some knowledge about the action of ganglion-blocking agents could be obtained in a population of healthy young adults, at the same time receiving training in making clinical observations and in rendering these observations quantitative. The students worked in groups of four, with one student as subject and the remaining three as observers dividing the various duties among themselves. A set of observations was made every 20 minutes, timed with a stop-clock, in the following order: supine blood pressure and pulse rate; standing blood pressure and pulse rate; skin temperature, body temperature, and room temperature; salivary secretion and sweating rate; ocular accommodation and reaction to light. This sequence was strictly followed, so that the interval between successive particular types of observation was kept constant. Two sets of control observations were made before injection of the drug, the subject having been instructed to take a light lunch, not to drink too much, and to empty his bladder. Immediately after the second set of control observations, 25 mg. of hexamethonium bromide was injected subcutaneously into the deltoid area.

The most common effect was a fall in body temperature (90% incidence) and rise in skin temperature (76%); and then (in descending order of frequency), fall in supine and standing systolic blood pressure, rise in supine and standing pulse rate and reduction in salivary secretion, and reduction in the reaction of the pupil to light and to accommodation (30-40% incidence). Sweating was also reduced. The incidence of ganglionic block over the various autonomic functions tested was different in every one of the 41 subjects for whom complete records were obtained. Variability in the response to a ganglion-blocking agent is as great in normal subjects as in patients. It may be regarded as a result of the varying autonomic constitution of different individuals.

Acute Renal Failure During Pentolinium Therapy. A. B. Carter and R. W. Payne. Lancet 2:537-539 (Sept. 15) 1956 [London, England].

Carter and Payne report the histories of two men, aged 60 and 46, respectively, in whom acute renal failure developed while they were being treated for hypertension with pentolinium tartrate (Ansolysen). The type of renal failure suggested an initial lowered filtration rate associated with prolonged hypotension followed by failure of tubular function. These two cases suggest that the continued use of pentolinium tartrate may be dangerous to elderly patients, although the usual side-effects of postural vertigo, constipation, and dryness of mouth may be absent. The use of pentolinium in the elderly can be justified only as a life-saving measure in cases of left ventricular failure, progressive gross retinal changes, or continuing hypertensive encephalopathy. The patient should be instructed to watch for listlessness, drowsiness, or any diminution in volume of urine and thereupon to stop taking the tablets. Once renal failure is suspected in a patient receiving pentolinium tartrate and the drug has been withdrawn, it is important to restore circulation as quickly as possible by raising the blood pressure. An intramuscular injection of 10 mg. of methedrine sulphate was effective in each case. Care should be used in prescribing larger doses because hypertensive patients remain very susceptible to methedrine even when they are in hypotension. Once the blood pressure has become reasonable, the treatment should be as for anuria from other causes.

Breast Cancer and Heptaldehyde (Preliminary Report). R. N. Lawson, A. L. Saunders and R. D. Cowen. Canad. M. A. J. 75: 488-488 (Sept. 15) 1956 [Toronto, Canada].

The rarity of cancer of the breast in Eskimo women in Canada has led to an investigation of their mode of life. The most striking aspect of their diet is the high proportion of fat, much of which is consumed in a frankly rancid state. Heptaldehyde is one of the chemical factors found in rancid fat. Earlier investigators had observed that when this substance is added to the diet of mice harboring spontaneous carcinomas of the mammary gland, liquefaction and regressive changes of the tumors resulted without apparent injury to the animals. The authors studied the toxicity of heptaldehyde in rats, demonstrating the fact that the lethal dose in 200-gm. rats was between 4 and 5 cc. They have given over 300 doses of 1 cc. each to human patients without any apparent ill-effects. They have used as much as 3 cc. but have confined the maximum quantity to 1 cc. in any single injection site.

Two patients with inoperable metastatic breast cancer were given intragluteal injections of heptaldehyde at intervals of one week. Both patients experienced a painful response in the site

of the malignant tumor within five minutes of the intragluteal injection. The areas of the breast surrounding the tumor did not become tender. Tumor growth appeared to be immediately arrested. After eight weeks, treatment was discontinued, as the pain phenomenon in the tumors was cumulative. Tenderness and pain in the tumor nodules increased with repeated doses and persisted for longer periods. Three weeks after cessation of treatment, one patient was given 300 mg. of testosterone. Within 24 hours all the tumor areas visibly increased in size, and she died five days later. The other patient underwent simple mastectomy, and she is now alive and free of gross disease 10 months after treatment. Extending the studies to other patients with breast cancer, the authors found that four-fifths experienced a pain reaction within the tumor within from four to eight minutes after the injection. On several occasions when the drug inadvertently entered the blood stream, as evidenced by a rancid taste in the mouth and pain in the breast tumor, there was a distinct drop in skin temperature over the cancer within 10 minutes of the injection. Since no demonstrable thermal changes were noted after administering heptaldehyde in any case of benign or inflammatory breast disease, it would appear that this phenomenon could be a useful clinical test for breast cancer.

Symptomatology and Pathogenesis of Intoxication with Penicillin Ester. G. Wichmann, E. Koch and F. Heiss. Ztschr. klin. Med. 154:111-125 (No. 2) 1956 (In German) [Berlin, Germany].

Experiments were carried out on guinea pigs and rats given injections of the hydriodide of the diethylaminoethyl ester of penicillin by the intramuscular, intracardiac, and intracerebral routes and into the carotid arteries. Similar experiments had previously been made with sodium penicillin G. Three standard syndromes of intoxication were observed in both guinea pigs and rats after the administration of the penicillin ester: acute generalized tonic-clonic spasms, acute diffuse pulmonary edema with pulmonary hemorrhages, and enterocolitis with a protracted course and terminal collapse. Acute generalized spasms and acute pulmonary edema were produced in the animals by the intramuscular administration of the penicillin ester, but these acute syndromes were not produced when sodium penicillin G was given by this route; they were, however, produced by both penicillin ester and sodium penicillin G when given by the intracerebral route or into the carotid arteries. The severity of the intoxication syndrome that occurred in the animals after the administration of the penicillin ester always depended on the degree of concentration of the penicillin ester in the cerebral tissue. It appears that the penicillin ester passes the blood-brain barrier in the animals and that the penicillinase activity in the cerebral tissue is temporarily inhibited. The results are a breaking-down of ganglion cells, acute spasm syndromes, and pulmonary edema. A review of the literature showed that after the administration of penicillin ester preparations to human beings the incidence of symptoms of intoxication was 130 times higher than after the administration of procaine penicillin preparations.

Jensen and Hallas-Moller and his Danish co-workers reported that the concentration of the penicillin ester in the pulmonary tissue of guinea pigs was three times higher than that in the blood, while the pulmonary tissue concentration of the penicillin G alone, which has an antibiotic effect apart from the ester compound, was not higher than its concentration in the blood. The authors' observations in the course of their experiments in animals and reports in the literature of observations in man establish the fact that the pulmonary affinity for the penicillin ester in animals and in man applies only to the ester itself, while the concentration of the penicillin freed from the ester compound is about the same in the pulmonary tissue and in the blood.

Penicillin ester preparations have been recommended for the treatment of patients with inflammatory cerebral disturbances, pneumococcic and meningococcic meningitis, and inflammatory diseases of the lungs. From the viewpoint of the greatest usefulness and the least damage, penicillin ester preparations are definitely inferior to sodium penicillin G in the treatment of all of these diseases.

ANESTHESIA

Roentgen Therapy and Cyclopropane Sensitivity. P. A. Foster. Anesthesiology 17:735-738 (Sept.-Oct.) 1956 [Philadelphia].

A 39-year-old man received a course of deep roentgen therapy for carcinoma of the floor of the mouth. The irradiation was completed five weeks before an operation was scheduled. There had been no radiation sickness, and the patient had been able to eat, had not lost much weight, and was in good general condition. A two-stage operation was planned in which suitable skin pedicle grafts would first be fashioned for use at the second stage when reconstruction of the lower jaw was to be carried out after resection of part of the mandible. It proved impossible to maintain this patient on cyclopropane because of extreme sensitivity. After a flow of this gas of 200 ml. per minute had been allowed to enter the closed circuit for two or three minutes, respiratory arrest followed that lasted for approximately half an hour. Pulse and blood pressure, however, were relatively unaffected. Eventually, the use of cyclopropane was discontinued, and nitrous oxide with minimal ether, and Demerol intravenously, was substituted. He did not prove unduly sensitive to this combination, tolerating amounts that experience suggested was normal for a person of his age and sex. Recovery was uneventful after the surgery, which took five and one-half hours.

An extreme sensitivity to cyclopropane may be shown by elderly people, especially if their premedication has included a respiratory depressant, but it is not usually seen in younger adults. The selective depression of respiration with poor analgesia in this 39-year-old man is regarded as significant because it has been observed that animals exposed to roentgenization of the whole body show an especially poor tolerance for cyclopropane but not for ether, ethylene, nitrous oxide, or thiopental sodium. Radiation therapy would probably not have such an effect on human beings unless the cerebrospinal axis is in the path of the beam. It is suggested that irradiation around the head may increase the permeability of intracranial vessels, thereby allowing entry to certain drugs (for example, relaxants) that are normally excluded by the blood-brain barrier. Drugs that normally penetrate may do so in greater degree. The peculiar pattern of neuronal radiation damage seen suggests that an excessive vagal tone may increase the hazards of intubation with cyclopropane, that consciousness may be more easily depressed, and that disturbances of temperature regulation may be encountered. Unusual responses to anesthesia following radiation therapy have received little attention in the literature. They may prove important during the treatment of casualties following an atomic explosion.

Control of Postoperative Vomiting with Marezine: A Double Blind Study. D. C. Moore, L. D. Bridenbaugh, V. F. Piccioni and others. Anesthesiology 17:690-695 (Sept.-Oct. 1956 [Philadelphia].

The effectiveness of parenteral injections of Marezine (cyclizine lactate) to control postoperative vomiting was investigated with a method that has been developed as a standard for antiemetic drugs. The cyclizine is injected intramuscularly when the patient is taken to the operating room, again intramuscularly on return from the operating room, and then intramuscularly every four hours for four doses. In this experiment, 1 cc. of solution was injected each time. The cyclizine solution contained 50 mg. of the drug per cubic centimeter. During a double-blind study on 276 patients, who were operated on under various types of anesthesia, it became evident that cyclizine lactate significantly reduced the incidence of postoperative vomiting. This would seem to substantiate previous reports, which had asserted the effectiveness of cyclizine but had not employed the double-blind technique in evaluating the drug.

BOOK REVIEWS

Medical Effects of the Atomic Bomb in Japan. Edited by Ashley W. Oughterson, Clinical Professor of Surgery, Yale University School of Medicine, New Haven, and Shields Warren, Pathologist, New England Deaconess Hospital, Boston. National Nuclear Energy Series, Manhattan Project Technical Section, Division VIII—Volume 8. Cloth. $8. Pp. 477, with illustrations. McGraw-Hill Book Company, Inc., 330 W. 42nd St., New York 36; 95 Farringdon St., London, E.C.4, England, 1956.

This well-illustrated and well-documented book concerning the medical effects of weapons that have altered history and our way of life should be of great interest to physicians throughout the world. The first chapter contains an excellent summary of findings, which are afterward documented in detail in appropriate chapters. The book is fairly comprehensive in that it describes the prelude to the work and the scope of damage and effects on medical care and facilities, presents statistical data on population and casualties, and discusses medical aspects from the viewpoint of the clinical observer, the hematologist, and the pathologist. Six appendixes, dealing with subjects such as organization and personnel, materials and methods, population, and statistical data, afford more specific information concerning the studies reported in the text. The index is weak. The book is literally crowded with facts and material that one may study for hours. Perusal of the summary chapter and selected reading of other portions will rapidly acquaint the medical reader with the general and specific medical problems of nuclear warfare. The colored plates vividly depict the injuries. Some of the photographs are reproduced from early Japanese military reports which illustrate early findings that United States survey personnel did not observe because of their arrival in the areas weeks after the bombings. This is a valuable book for background and reference for physicians concerned with the medical aspects of nuclear warfare and, in addition, for persons engaged in military medicine, which includes those who are concerned or who should be concerned with the medical aspects of civil defense—namely, all physicians.

The Administration of Health Insurance in Canada. By Malcolm G. Taylor. Cloth. $3.85. Pp. 270, with 5 illustrations. Oxford University Press, 114 Fifth Ave., New York 11; Amen House, Toronto, Canada; Amen House, Warwick Sq., London, E.C.4, England, 1956.

Today about 50% of Canada's population is enrolled in some type of health insurance plan. With attention concentrated primarily on the Blue Cross hospital care plans, the medical care plans sponsored by the provincial medical associations, and the hospital and social assistance medical care programs operated by the government, this study encompasses a total of 24 specific insurance plans. An evaluation of the various plans is based on detailed examination and description of the differing objectives, achievements, and problems of each type of plan. In developing his central theme of the task of administering health insurance, the author discusses extensively such matters as the determination of benefits and premiums and the effects of the individual plans on the physicians, hospitals, and patients involved. The author's personal observation provides the principal basis for a substantial part of the text. The 38 tables and figures that appear in the book and the numerous text tables serve as helpful supplements to the written text. Much of the tabulated material, however, is not fully documented with specific references to exact sources and/or to the author's method in arriving at statistics.

The Canadian Blue Cross plans, modeled after those developed in the United States, operate on the service benefit principle whereby a maximum number of days of hospital care per year plus necessary extras (operating room, drugs, and dressings) are provided. The five Blue Cross plans operative in Canada are coordinated by the Canadian Council of Blue Cross Plans. In addition to their hospital care benefits, three of the plans offer a limited medical and surgical benefits contract of the indemnity type. In 1954 about 3,255,000 people were enrolled in Blue Cross plans for hospital benefits, and 1,027,000 for medical and surgical indemnity benefits. The profession-sponsored medical care plans also provide benefits on a service basis. In contrast to most of the profession-sponsored plans in the United States, many of the Canadian plans offer home and office calls by physicians as benefits. The physicians accept a 10% reduction in fees to cover administrative costs. These plans cover 1,353,000 persons. Government-sponsored hospital care plans have been established in four Canadian provinces in which total enrollment in 1954 was 2,698,000 persons. The Swift Current Medical Care Plan is the only example of a government-sponsored program covering all the residents of a large area (about 50,000 people in southeastern Saskatchewan reside in the region served by the Swift plan). This comprehensive medical care program is supported by taxes levied on all residents and provides payment to physicians on a fee-for-service, contract-schedule basis. Public medical care plans apply only to those groups in the population receiving social assistance of some sort. The number of such beneficiaries in 1953-1954 was 293,792.

One of the most serious problems facing government-sponsored plans concerns enrollment, which must necessarily encompass the entire population. The absence of the promotional function does not counteract the obstacles that obligatory comprehensive and simultaneous registration and tax payment present. In Canada today, all of the 10 provinces exercise some degree of supervision over all of the hospital and medical care programs. While the amount and type of supervision varies from province to province, in the author's opinion, successful administration will soon necessitate a degree of uniformity. Taylor describes the position of the physician in private practice as "anomalous"—on the one hand, he is a confidant and an alleviator of pain; on the other hand, he "is a prime example of the small businessman with fixed and variable costs in operating his practice whose income is the difference between his revenue and expenditures." In the author's thinking, these two functions tend to conflict. He believes that the physician, in asking remuneration for his services, counteracts his beneficial work by inciting worry, fear, and "continuance of the state of ill-health." In respect to this, Taylor quotes Stern who says, "the attitude of the lay public is that the physician is the beneficiary of another's misery." It is on the basis of this premise that the main criticism of the book can be promulgated. While the physician feels entitled to just remuneration, his primary role is that of a professional servant and not that of a tradesman or businessman. To equate the two roles is to misinterpret the function of the private physician, as well as to miscalculate his own conception of his role in society. Although an economic factor does exist in the doctor-patient relationship, it can be contended that this element is subordinate to the quality of care that the physician strives to provide.

Taylor points out that administrative regulations are time-consuming and irritating to the physician, but he also implies that such disadvantages are offset by the advantages of being able to offer whatever treatment the physician believes necessary without concern over the patients' ability to pay. It should be remembered that this advantage is greatly limited by the extent of the patients' insurance coverage. In conclusion, the author points out that governmental controls are the lesser of two evils, the greater being unpredictable and frequently unmanageable medical bills. This view would appear to be an oversimplification of the problem. Aside from the inevitability of the economic factor in medical care (which is an essential factor regardless of whether health insurance is available), the principal problem to be resolved in regard to health insurance would seemingly involve an evaluation of the effect of controls on the quality of medical care. Physicians believe that further controls would be detrimental, indicating that Taylor's "two evils" have been ill-defined. The medical profession believes that any form of contractual practice is unethical to the extent that it results in a deterioration of the quality of the medical services rendered; thus, the effects of increased nonmedical control on the quality of medical care seem to the physician an unreasonably high price to pay for the opportunity to "budget medical care expenditures."

These book reviews have been prepared by competent authorities but do not represent the opinions of any medical or other organization unless specifically so stated.

Techniques and Procedures of Anesthesia. By John Adriani, M.D., Director, Department of Anesthesiology, Charity Hospital, New Orleans. Second edition. Cloth. $8.75. Pp. 568, with 192 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto, 2B, Canada, 1956.

This second revised edition of a popular textbook follows the purpose of the first edition, namely, to provide an outline for students of anesthesiology. The important points are presented in a concise but comprehensive manner. The text is divided into 10 parts. The first consists, after a few definitions, of tables giving the general properties of anesthetic drugs, and suggestions for selecting procedures of giving anesthetics for operations on the different regions of the body and drugs to be used when the most commonly encountered clinical conditions are met. Much of this material is from the author's book, "Selection of Anesthesia." The recommendations made are presented in outline form, and the justification for them is supported not by discussion but simply with a brief remark. This part also includes discussion of preanesthetic medication, a subject presently undergoing radical changes with the introduction of new drugs and new concepts. The recommendations given here reflect the recent teaching on this subject but not necessarily the latest methods. There is also a discussion of records of anesthesia and their preparation.

The second part is devoted to inhalation anesthesia. It briefly describes the drugs used and particularly the appliances. The use of the latter is covered in some detail with many photographic illustrations. This section covers the use of endotracheal equipment also. The classic signs of anesthesia of Guedel are given, although in present practices they alone are not sufficient to guide the clinician in determining the depth of anesthesia. The third part covers the complications of anesthesia and gives sound recommendations for avoiding and managing them. Basal narcosis with intravenous injections and rectal anesthesia are the subjects of the next two parts, followed by a section on regional anesthesia. Although this section covers one-fifth of the book and is fairly well illustrated, it provides the student with too little information to be of much value. Many of the most recent practices have not been included and some of the recommendations are debatable. For example, the author implies that blocks, excepting skin wheals, are best done with 22-gauge or larger size needles.

Specialized procedures occupy the next part, including pediatric, geriatric, thoracic, and obstetric methods. Little can be done with any of these subjects within the limited space allotted, therefore the text attempts little more than an outline of suggested procedures that are essentially the same as those already described. Recovery rooms are given some space in the final pages of this section. In the last two parts, resuscitation and inhalation therapy are considered. There is an appendix with clinical laboratory values and a good index. A brief bibliography is found at the end of each discussion. The illustrations show various types of equipment and their use. The book is an example of excellent design and printing. The author is to be congratulated on packing into so few pages the vast number of subjects included. Although the outline form will appeal to many, the book will probably be most useful to those beginning the study of this subject and possibly to those anticipating examinations by qualifying boards.

Epilepsy and the Law: A Proposal for Legal Reform in the Light of Medical Progress. By Roscoe L. Barrow, Dean, University of Cincinnati College of Law, Cincinnati, and Howard D. Fabing, M.D., Chairman, Legislation Committee, American League against Epilepsy. Cloth. $5.50. Pp. 177. Paul B. Hoeber, Inc. (medical book department of Harper & Brothers), 49 E. 33rd St., New York 16, 1956.

This book is described on the title page as being "a proposal for legal reform in the light of medical progress," but Dr. Pearce Bailey, in his foreword, recognizes that, for all its scholarship, this book is part of the literature of indignation. If all who read the book are as aware as was Dr. Bailey of the easily discernible use of half-truths and innuendo in seeking to appeal to the reader's emotions, then more good than harm should come from a widespread reading of it. The authors sincerely contend that medical progress in the control of epileptic seizures has outmoded our epilepsy laws. Four principal areas of complaint are covered: marriage license laws, sterilization laws, driver's license laws, and workmen's compensation laws. The best case is made for the first two. From the material presented, there seems to be little doubt that epilepsy is not the same as idiocy and insanity and that there is no eugenic reason for treating them in the same manner. It also appears that epilepsy is not an inherited disease. Society, therefore, will not suffer by permitting epileptics to marry and by eliminating epileptics from the purview of the eugenic sterilization laws. Granting the foregoing and granting that down through the years an unfortunate social stigma has attached to epilepsy, the authors are not able to present quite as good a case for amending the driver's license or workman's compensation laws. A driver who has an epileptic attack while driving 60 mph on a busy highway and an epileptic who drops one end of a heavy box that he is lifting with a fellow employee can cause serious injury to those other than himself. More than mere social stigma is involved. The authors do, however, insist that the privileges that they seek for the epileptic must be limited to the epileptic who is free from seizures and under a physician's care. Like most "literature of indignation," this book will find violent supporters and violent opponents. On the whole, however, it furnishes a valuable addition to the literature on the subject and may help to elevate the status of the epileptic in some degree. The appendix contains examples of the type of laws the authors believe should be enacted, and there is a commendably complete index, bibliography, and citation of legal references.

Management of Emotional Problems in Medical Practice. Edited by Samuel Liebman, M.D., Medical Director, North Shore Health Resort, Winnetka, Ill. Cloth. $5. Pp. 132. J. B. Lippincott Company, 227-231 S. Sixth St., Philadelphia 5; 2083 Guy St., Montreal, Canada; [British agent—Pitman Medical Publishing Co., Ltd., 39 Parker St., Kingsway, London, W.C.2, England], 1956.

This volume is the second in a series based on lectures given at the North Shore Health Resort, Winnetka, Ill., by nine distinguished physicians. Each lecture presents practical approaches to the management of the emotional problems treated daily by the medical practitioner. Dr. Karl M. Bowman's paper on psychiatric emergencies or what to do before the psychiatrist comes is full of good practical sense and gives special consideration to the violent patient and the suicidal patient, and how to manage problems of drug intoxication, refusal to eat, panic states, and hysterical states. Dr. Francis J. Gerty gives excellent advice on the use and abuse of sedatives and stimulants. Dr. Lewis Robbins considers the management of the anxious patient and takes up the symptoms, psychodynamics, and management of anxiety. The depressed patient, his understanding and management, is extremely well presented by Dr. Franklin G. Ebaugh. The management of emotional reactions in the male involutional period is covered by Dr. Otto Billig. The management of the multiple complainer by George C. Ham is an example of excellently applied practical psychiatry. Dr. Leo H. Bartemeier's paper on the management of overeating, overdrinking, and oversmoking considers overindulgence as a symptom of emotional disturbance. Dr. Walter C. Alvarez tells how to avoid the production of iatrogenic disease. He believes that anxiety neuroses are sometimes produced inadvertently by physicians and urges the physician to be optimistic, constantly to guard his tongue, especially in the presence of a hypochondriacal patient, and to avoid thinking out loud in alarming diagnostic medical terms. A concluding paper by Dr. Marc H. Hollender emphasizes the utilization of community resources in medical practice. This book is lucid, compact, practical, and clearly written. It is highly recommended.

Surgery of the Hand. By Sterling Bunnell, M.D., Consultant to Surgeon General of U. S. Army, to U. S. Navy, and to Alaska Department of Health. Third edition. Cloth. $22.50. Pp. 1079, with 1056 illustrations. J. B. Lippincott Company, 227-231 S. Sixth St., Philadelphia 5; 2083 Guy St., Montreal, Canada; Pitman Medical Publishing Co., Ltd., Pitman House, 39-41 Parker St., Kingsway, London, W.C.2, England, 1956.

The third edition of this excellent book has been greatly enlarged to include many recent advances in hand surgery. In the past, it has been through this book, as well as through the author's personal stimulus, that hand surgery has reached its present high plane. The parts dealing with the use of antibiotics for infections of the hand has been greatly expanded. Other new or improved chapters include those on postoperative treatment for the repair of tendons and on burns. The format of the book is similar to that of previous editions, but its increased size makes it a bit heavy to hold while reading. If future editions entail further expansion, the author should consider publishing it in two volumes. This book is highly recommended for all those doing hand surgery and should be in the libraries of all hospitals and medical schools. It is an excellent reference book for all levels of teaching, including the postgraduate level.

Ciba Foundation Colloquia on Ageing. Volume 2: Ageing in Transient Tissues. Editors for Ciba Foundation: G. E. W. Wolstenholme, O.B.E., M.A., M.B., and Elaine C. P. Millar, A.H.W.C., A.R.I.C. Cloth. $6.75. Pp. 303, with 96 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6; J. & A. Churchill, Ltd., 104 Gloucester Pl., Portman Sq., London, W.1, England, 1958.

This small volume is the second of a series to be published annually under the auspices of the Ciba Foundation of London dealing with basic research relevant to the problems of aging. The first volume was a colloquium on general aspects of aging. The present one is devoted to the aging of transient tissues, the normal life of which is shorter than that of the organism as a whole. The program is truly international in character. The 27 participants from both the United States and abroad are eminent authorities in their respective fields of anatomy, embryology, physiology, biochemistry, biology, zoology, and botany. Those interested in aging should find delight in the comprehensive conversational manner in which the subject is covered in this symposium. It is difficult to select any one part that is more interesting than another. Perhaps those who do not feel entirely at home with the highly scientific and technical approach to the subjects presented would be engrossed especially by those parts dealing with the regenerative capacity of ovarian tissues, mitochondrial changes in different physiological states, morphological aspects of aging in the placenta, chronological changes in placental function, biochemical evidence of aging in the placenta, aging of the axillary apocrine sweat glands in women, and aging in human red blood cells. One would not do justice to this volume if particular attention were not called to the exceptional artistic merit of the illustrations accompanying the articles. The discussions of the presentations in these colloquiums lend extraordinary value and interest to the program. The informal participation by the audience and the effective but not rigid control of the symposium by the chairman might serve as a pattern for other groups, the meetings of which are so often unenlightening because of their stereotyped panel or conventional order.

Clinical Urology. Volumes I and II. By Oswald Swinney Lowsley, A.B., M.D., F.A.C.S., President and Director, Oswald Swinney Lowsley Foundation, Inc., St. Clare's Hospital, New York, and Thomas Joseph Kirwin, M.A., M.S., M.D., Professor of Urology, New York Medical College, New York City. Third edition. Cloth. $32.50. Pp. 484; 485-985, with 590 illustrations by William P. Didusch. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1958.

In this edition, chapters 1 to 5 deal with the usual, well-accepted diagnostic procedures in urology. This is followed by a good, informative chapter on anesthesiology. In chapters 7 through 34, all the various diseases of each organ of the urogenital system are discussed in a well-organized and well-documented manner. The pattern followed in the discussion of these diseases is comprehensive and to the point. Detail does not succumb to verbosity. In chapter 35 the recent advances made in the field of antibiotic therapy are discussed. Here the reader will find treated the indications, contraindications, and efficacy of the various antibiotics in the treatment of infections of the genitourinary system. Each volume contains an index to the text and illustrations. The publishers have done their part very well. The quality of the paper and the arrangement of the pages into three columns facilitates reading. Since the publication of the second edition, many advances have occurred in urology which are all well documented in this edition. These two volumes are a combination textbook, encyclopedia, and atlas of urologic pathology and surgical techniques, profusely illustrated. The present edition assures for the volumes a continuingly prominent place in urologic literature. They can be unhesitatingly recommended not only as a textbook for students, interns, and residents but also as a reference book for the practitioner, surgeon, and urologist. It is unfortunate that the death of the senior author of this edition came before he had an opportunity to see the finished product.

Electrocardiographic Test Book. Volumes I and II. Paper, loose-leaf. $5 per set. Pp. 107; 132, with illustrations. American Heart Association, Inc., 44 E. 23rd St., New York 10, 1958.

The purpose of this book is to assist students in the study of electrocardiography. The presentation in volume I consists of 110 selected electrocardiograms reproduced as examples of normal and abnormal varieties, together with questions. The answers, documented and discussed on the basis of clinical and roentgenologic data, are assembled on the corresponding pages in volume II. In addition, the two volumes contain general questions and answers pertaining to electrocardiographic differential diagnosis; tables of normal measurements, mostly compiled from the literature and some thus far unpublished; and a comprehensive index. This original approach to teaching clinical electrocardiography should serve the limited aims of the authors, although objections can be raised concerning the examples selected, the interpretation of some of the records, and the illogical questions posed in conjunction with some of the records. There are some inconsistencies in dealing with the difficult problem of differentiation of ischemic alterations from those caused by heart strain and hypertrophy (figures 3 and 24). One also wonders whether statements like the one on page 39 of volume II, "with posterior infarction there is a tendency for the T-waves to become lower and inverted in lead I and positive in lead III," were really acceptable to the advisory and review panel of 28 distinguished authorities. The publication deserves the highest commendation for the excellence and clearness of the reproductions of electrocardiograms and the simplicity and conciseness of the accompanying text that make these volumes most valuable to anyone concerned with learning or teaching clinical electrocardiography.

Studies in Topectomy. Edited by Nolan D. C. Lewis, M.D., Carney Landis, Ph.D., D.Sc., and H. E. King, Ph.D. Cloth. $6.75. Pp. 248, with illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16; 99 Great Russell St., London, W.C.1, England, 1958.

The New York Associates in Brain Research explored in 1948 to 1949 the potentialities of psychosurgical methods as a therapy for mental disorder. They used topectomy of the frontal lobes on 66 patients, many of whom were chosen for the severity of their mental disorder. The operations, both frontal ablations, performed bilaterally, were of two types, one removing the superior portion and the other the more orbital section of the lobe. There was no operative mortality or lasting neurological changes. Psychiatric evaluation was undertaken about two years after the operation. The results were not impressive. The procedure was considered of limited value for chronic schizophrenics but of slight usefulness for chronic psychoneurotics and for some of the patients with manic-depressive reactions and with involutional psychoses. An independent psychiatric evaluation by another group of investigators was even less enthusiastic, and concluded from the strictly therapeutic viewpoint that the verdict at best would have to be "not proved." In general the importance of applying therapeutic measures, even topectomy, before the psychotic process has become fixed, was emphasized. The study was carefully planned and executed by a skilled research team. The report reflects their high standards and excellent tallying of the results. The details of the surgical technique, psychometric studies, vestibular function test, and other investigative methods are reported fully and clearly. Although it is published five years after the end of the project, the book is a valuable contribution to our knowledge of topectomy and its effect on psychiatric disease.

Textbook of Gynecology. By Emil Novak, A.B., M.D., D.Sc., Gynecologist-in-chief, Bon Secours Hospital, Baltimore, and Edmund R. Novak, A.B., M.D., F.A.C.S., Instructor in Gynecology, Johns Hopkins Medical School, Baltimore. Fifth edition. Cloth. $11. Pp. 940, with 543 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1958.

This popular book did not need much revision to bring it up to date. The few important contributions to gynecology made in the last four years are included. The chapter on uterine cancer was entirely rewritten because of the controversy concerning carcinoma in situ. Likewise, the chapter on pelvic tuberculosis was completely rewritten because of advances in both diagnosis and treatment of the disease. The authors mention the new skin biopsy tests for sex determination. They consider kraurosis and leukoplakia of the vulva together because of the frequency with which the two terms are wrongly applied and the existing confusion as to their differentiation. The authors do, however, make a rational distinction between the two conditions. There is a full description of carcinoma in situ, with emphasis on the difficulties in diagnosis. The authors again summarize the important essentials of the responsibilities of the general practitioner in the campaign against cervical cancer. In the chapter on tuberculosis of the generative organs, the place of streptomycin, aminosalicylic acid, and derivatives of isonicotinic acid is discussed. There is no doubt that the Novaks have again produced a classic book that should continue to be profitably studied throughout the world.

QUERIES AND MINOR NOTES

FETAL EFFECTS OF DEMEROL ANTE PARTUM

To the Editor:—*In the local hospital the use and dosage of Demerol in a woman in labor with an intrauterine pregnancy was questioned when an infant had a four-or-five minute delay in cry and respiration attempts. A review of the available literature reveals that it is the consensus that Demerol will not have a depressant effect on any infant, whether at term or premature. The mother had received a total of 200 mg. of Demerol within a three-hour period prior to the actual delivery. The last dose was 100 mg. and was given 20 minutes prior to delivery. How soon after injection can one normally expect a peak of effect in the infant (if any)? What is the maximum dose that could safely be given to a normal mother weighing 70 kg. (154.2 lb.) in labor without danger of depression to the baby? Is there any place in the literature indicating that morphine (given to the mother in labor) was not depressant to the baby?*

M.D., Wis.

Answer.—The depressant effect of Demerol on the fetus depends on certain variables that cannot be predicted in any given case. These variables include the tolerance of the mother, her weight, the rapidity of absorption from the injection site, and the type of anesthesia used for delivery. In general, the maximum effect of an intramuscular injection should occur about one hour after administration to the mother. This is rarely of clinical significance if conduction or local anesthesia is used. With general anesthesia, with cyclopropane or nitrous oxide ether, the narcotizing effect of this combination of drugs may be of significance to the baby. Most normal labors, of 6 to 10 hours' duration, can be readily managed with a single dose of 100 mg. of Demerol, preferably combined with scopolamine (hyoscine) in a dose of 0.4 mg. If this is inadequate to control the patient's discomfort, trichlorethylene (Trilene) inhalation or the judicious use of chlorpromazine or one of its derivatives is considered preferable to the repeated doses of Demerol. When repeated doses of narcotics of any type must be given for the control of pain in labor, when they are used at repeated irregular intervals for the purpose of obtaining rest in a prolonged labor, or when the mother shows a profound response to these drugs, their narcotizing effect upon the baby may be effectively and promptly minimized by the administration of amphetamine or nalorphine (Nalline) hydrochloride to the mother approximately 15 to 30 minutes prior to delivery. Morphine sulfate has been shown both clinically and experimentally to be a depressant to the baby. This consultant is unaware of any valid data to the contrary.

PREMATURE GRAY HAIR

To the Editor:—*In the May 19 issue of* The Journal, *page 299, is a query on graying of hair. Is there any known medication or treatment that will forestall or delay premature graying of hair? If not, what is a safe method for use in changing the color of the hair to its former color?*

M.D., South Carolina.

Answer.—There is no known medication or treatment that will forestall or delay premature graying of the hair. Reports of the effectiveness of pantothenic acid or *p*-aminobenzoic acid in delaying or lessening premature graying of the hair have never been proved. As far as a safe method of changing the color of the hair is concerned, there is no absolutely safe procedure. An occasional person will still react unfavorably to the methods mentioned subsequently. The metallic hair dyes are successful only when frequent applications are made, and the desired color may appear after a series of treatments that progressively darken the hair. The usual solutions contain silver, copper, iron, or lead, which act with the sulfur content of the hair to deposit a metallic sulfide on the shaft. Silver nitrate, in combination with a 1% solution of pyrogallic acid as a reducing agent, may be adopted for all shades from white or brown to black, depending on its strength. The synthetic organic dyes are also effective and are of two types. The first, or "azo" type, has a low index of sensitivity but has the disadvantage that several applications are necessary to obtain the desired shade. The most popular types of dyes are those of the amine or aniline type. They have two characteristics that render them superior to their predecessor: First, the desired color is usually acquired at one sitting. Second, the colors themselves offer a wide range of choice and are much more natural in appearance. Several preparations are on the market, and patch tests should be performed prior to their usage. This synthetic dye is usually sold in two bottles, of which one contains a 1 to 3% aqueous solution of the para dye and the second an oxidizer such as hydrogen peroxide or sodium persulfate or perborate. Some of these are available for home application, although it is usually preferable to have the applications made by a professional. Inasmuch as the chemicals employed are not easily handled by the amateur, the skill and experience of a careful operator should minimize the possibility of untoward side-effects.

ULTRAVIOLET BLOOD IRRADIATION

To the Editor:—*A 39-year-old man is being treated for "a general run-down condition." Apparently he is not progressing as well as anticipated. His brother has chronic bilateral thrombophlebitis of both legs and, in addition to saphenous vein ligations and anticoagulant therapy, he has received ultraviolet blood irradiation, possibly according to the Knott technique. It is stated that some improvement has followed this therapy. The treating physician for the first-mentioned man feels that ultraviolet blood irradiations may be of value in improving his patient's condition. I would appreciate an opinion on the efficacy of ultraviolet blood irradiation in regard to its application to the broad category of "general run-down condition."*

M.D., Massachusetts.

This inquiry was referred to two consultants, whose respective replies follow.—Ed.

Answer.—There is no objective evidence that ultraviolet irradiation of the blood by the Knott technique has any beneficial effects. It has been used widely for a great number of conditions, with purportedly uniform good results. The nature of the ultraviolet treatments is such that a great deal of psychotherapeutic benefit may ensue from their use. This, together with the enthusiasm of those who have used the treatments, probably accounts for the reported value of the technique. Its use for any patient with a "general run-down condition" is not indicated. It is essential to establish why a 39-year-old man is "run-down," so that rational therapy may be instituted.

Answer.—Ultraviolet blood irradiation enjoyed a brief display in the medical literature from 10 to 15 years ago. A portion of blood (about 250 cc.) was removed from a patient, citrated, and then, after exposure to powerful ultraviolet irradiation in a suitable irradiating chamber, was immediately pumped back into the venous system. While the claims of the favorable effects of hemoirradiation on bacterial infections did not violate credibility, in view of the known bactericidal potency of ultraviolet rays under suitable conditions, reports soon appeared suggesting the efficacy of hemoirradiation in acute thrombophlebitis, bronchial asthma (intrinsic), rheumatoid arthritis, osteoarthritis, postfebrile poliomyelitis, "non-healing" wounds (apparently due to chronic osteomyelitis or vascular insufficiency), and paralytic ileus. As a result of the alleged dramatic response of chronic as well as acute diseases, a hypothesis of "ultraviolet ray metabolism" was developed.

As often occurs in medicine, a reputedly successful, if not dramatic, new therapy in the hands of a few is quickly taken up by the many and applied to a wide array of conditions of

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The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications and queries on postal cards cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

unknown etiology in the hope of a cure. Hemoirradiation was no exception, and disappointment followed inevitably. More important, it stimulated well-controlled experiments in which bloods seeded with various pathogens were irradiated. These failed to corroborate the clinical reports. Indeed, in saline medium, where ultraviolet could be expected to reach the bacteria in more potent doses because of minimal absorption, irradiation also failed to eliminate the organisms. In nonbacterial diseases it was never proved that ultraviolet irradiation had an "energizing" effect on the body, and no satisfactory short-term or long follow-up proof on chronic arthritides and other conditions were published. The whole concept of this form of treatment, in fact, was never subjected to a well-controlled analysis free from objectionable methodology. Uncritical empiricism based on a tenuous and untested hypothesis may briefly lead to the unbridled use of an agent, even for such vague conditions as "general run-down condition." Today, ultraviolet hemoirradiation is a medical curiosity that did not fulfill the therapeutic claims originally made for it.

CAUSE OF DEATH

To the Editor:—*In "Collectivism on the Campus: The Battle for the Mind in American Colleges," by E. Merrill Root (New York, the Devin-Adair Co., 1955, p. 133), is a passage dealing with the death under mysterious circumstances of a young student in California. After an autopsy, the cause of death was given as inhibition. This matter was not discussed at length, but apparently it referred to such stimulation of the central nervous system by terror that nervous reflexes stopped the action of the heart and/or lungs. I would appreciate it if you would comment on this diagnosis.*

Thomas Parker, M.D., Greenville, S. C.

This inquiry was referred to two consultants, whose respective replies follow.—Ed.

Answer.—There are many instances in fiction and occasional, but unverified, references in scientific literature to sudden death during a period of extreme emotional stress. One might postulate, although it is extremely improbable, that sudden hypothalamic overactivity, in response to fear or some other emotion, might cause vagal stimulation to such a degree that it would bring about cardiac arrest and/or inhibition of respirations. This, however, has never been demonstrated or proved. One might question whether such a phenomenon, if it exists, could be related to the so-called acute brain death, which sometimes occurs without warning in schizophrenia and other so-called functional mental diseases. In this, however, there is usually a brief period of of extreme hyperpyrexia, motor hyperactivity, and either stupor or convulsions preceding death. In these cases, furthermore, extensive cellular alterations in the brain have been reported. Before answering this query, the original reference was reviewed. When the body of the subject was found, it was lying in a furnace pit near an unconnected gas heater. The gas that fed the furnaces was turned off, and the furnace room door was standing open. A few days later, as soon as an investigation began, the entire basement was flooded, and other possible clues were obliterated; apparently the flooding was purposely done. The only finding in the autopsy was pulmonary edema.

It is apparent, from the circumstances leading to death and the findings after death, as well as from lack of any proof of inhibition of purely psychic origin and not secondary to toxic or other organic stimulation of centers that depress cardiac and respiratory functions, that one must conclude that in this case the cause of death was not found. One must assume that external causes of toxic or other origin, which were not brought to light in what was apparently a very complete autopsy, were responsible for the death of the subject. It was the final conclusion that this was "death by homicide" (page 137). While inhibition may be a theoretical cause of death, it is not so accepted clinically. It would be better in cases like this to conclude, as was done in this case, that death was due to external causes. One should be willing to admit that the cause was not found and should not rely on intangible, unscientific explanations.

Answer.—The Standard Nomenclature of Diseases and Operations published by the American Medical Association does not list "inhibition" as a disease entity. Inhibition as a cause of death is not acceptable in medical circles and probably would not be accepted by boards of health on a death certificate. Many deaths occur under mysterious circumstances, and the cause in any one can be overlooked in an autopsy unless the examination covers all phases necessary to accomplish this.

TACHYCARDIA

To the Editor:—*A 75-year-old woman suffers from chronic suppurative bronchitis and asthma and is highly allergic to egg albumin. She has frequent attacks of tachycardia, which usually occur after dinner and may last half an hour. During the attack the pulse is about 120 per minute, full and tense, and there is shortness of breath and at times pain extending down the arms. Is there any therapeutic measure that might reduce the frequency of these attacks or give relief?*

M.D., New Jersey.

Answer.—It would be helpful to have more information concerning the nature of the tachycardia and the characteristics of the rate and rhythm. If there is any irregularity of the rhythm, then one must consider the possibility of a paroxysmal fibrillation or an atrial flutter with varying block. An electrocardiogram taken during an attack would help to settle this question.

If the rate is perfectly regular at 120 beats per minute, then the underlying mechanism is probably a normal sinus rhythm. Therefore, one must suspect that the underlying cause is coronary insufficiency, probably induced by the demands of digesting a heavy meal. Reducing the amount of food at the evening meal and dividing the total daily amount of food into four or five small meals may be helpful. Administration of glyceryl trinitrate (nitroglycerin), 1/200 grain (0.3 mg.) sublingually, may be tried at the onset of her attack. If the glyceryl trinitrate aborts the attack and relieves the dyspnea and pain, then the usual program for angina should be instituted. If it can be demonstrated that the attack is a paroxysmal type of fibrillation or atrial flutter with varying block, then administration of quinidine sulfate, 200 mg. after meals and at bedtime, is indicated in an effort to prevent the attacks. An additional 200-mg. tablet may be given during the attack. In spite of the highly allergic background of the patient, it is doubtful that any allergic reaction is playing a role in the attacks.

AZOOSPERMIA

To the Editor:—*Examination of a 34-year-old man was essentially negative apart from slight obesity. Urinalysis and serology were negative. A fertility investigation by a urologist revealed azoospermia. The patient asks: "I was working with a poison gas unit during the war—could this have caused me to be sterile?"*

Thomas W. Parkinson, M.D., Gastonia, N. C.

Answer.—The germinal epithelium of the testes may be severely damaged as a result of repeated absorption of small doses of toxic substances over a long period of time through the skin, lungs, or alimentary tract. Alcohol and morphine are known to act in this way. Various industrial poisons have been inculpated in the same respect, among them lead, mercury, sulfocarbonate, benzene (benzol), toluene (toluol), phosphorus, and turpentine. This consultant has no information about the chemistry of the gases used in warfare or about the precautions taken to protect men working with them. There would seem to be at least a theoretical possibility that the spermatogenic apparatus might be exposed to injury. Further investigation is needed to throw light on the cause of azoospermia in this patient. Testicular biopsy may show normal spermatogenesis, and in that event the trouble is obviously a blockade in the duct system; it may reveal aplasia or hypoplasia of the seminiferous tubules; it may show germinal epithelium that is histologically fairly normal but functionally inactive, and if at the same time hormone assays demonstrate a low level of gonadotropins the diagnosis of pituitary eunuchoidism is apparent. In all of the foregoing cases the primary cause of azoospermia would be adequately explained by the findings and is clearly unrelated to any sort of chronic intoxication. However, if the biopsy finding is sclerosing tubular degeneration and atrophy, one may consider the possibility that a toxic factor was initially responsible, though this is by no means proved by the evidence obtained.

BRONCHIAL ASTHMA WITH TUBERCULOSIS

To the Editor:—*How frequently does bronchial asthma occur with pulmonary tuberculosis? A number of patients in all the different stages of pulmonary tuberculosis have all the classic signs of bronchial asthma. Are the physical signs and symptoms due to bronchial asthma, per se, or are they the result of intermittent flaring up of the tuberculous process? During these episodes these patients have been given the usual treatment for bronchial asthma and this has relieved them. Is there some other treatment? Is this an allergic manifestation to the tubercle bacilli?* *M.D., Philippines.*

Answer.—The incidence of bronchial asthma in patients with pulmonary tuberculosis is identical with its incidence in the general population. This represents true allergic bronchial asthma, with the sensitivity being due to the common antigens, and does not represent an allergic manifestation to the tubercle bacilli. The conventional treatment for asthma is indicated and should produce results uniform with those obtained in non-tuberculous patients. The only exception to this statement is that steroid therapy should not be used in those patients having known tuberculosis or in those suspected of having tuberculosis. It is also true that the physical signs and symptoms of bronchial asthma may occur in patients with pulmonary tuberculosis and be due to the tuberculosis and not to allergic bronchial asthma. In these patients, the common cause for these findings is due to involvement of the bronchus by either a tuberculous bronchitis and/or pressure on the bronchus by an enlarged mediastinal lymph gland. These patients will also show a response to the conventional therapy with bronchodilator drugs, but this response will be only temporary and symptomatic and therefore this therapy must be accompanied by therapy with antimicrobial drugs.

DRUG ADDICTION

To the Editor:—*A 45-year-old male patient with osteoarthritis takes the following amounts of medication nightly in order to obtain satisfactory rest: codeine, ½ to 1 grain (30 to 60 mg.); three to four Bufferin tablets; and one or two Valmid tablets. Is there any danger of addiction or other harm from continued use of the above?* *M.D., New Hampshire.*

Answer.—The danger of addiction in the case described depends primarily on the personality structure of the patient. If he is a mature, emotionally stable individual, the danger of addiction would be remote. On the other hand, if he is an unstable person there would be some danger of addiction to codeine. Indications that addiction might be developing would be requests for increase in amounts of codeine or attempts to obtain supplies without obtaining new prescriptions and by obtaining prescriptions from more than one physician. This danger, which is slight, is further minimized if close contact with the patient and with his family can be maintained. There should be no harm from continued use of either the codeine or Bufferin. Sufficient information concerning idiosyncrasies to Valmid is not available to evaluate the danger of long-continued use of this particular substance. If the patient can be examined at frequent intervals, any untoward drug intoxication should be detected before significant harm is done.

TRAUMATIC AMPUTATION OF FINGER TIP

To the Editor:—*What would be an approved method for immediate definitive treatment of a 35-year-old aircraft factory worker whose injury consisted of an almost complete guillotine type of crushing amputation, bone and soft parts, of the right index finger, through the base of the distal phalanx, involving the distal joint? There remained only a slight subcutaneous bridge attaching the amputated end to the balance of the digit? All major digital vessels apparently had been severed, as there was no bleeding from the distal stump, while the proximal end bled freely.* *M.D., California.*

Answer.—Replacement of the tip of the finger would, in all probability, not be successful, as the bulk of the tissue was too great and the injury was a crushing one. If the skin of the pulp was not too crushed, all the subcutaneous fat could be removed and the skin of the pulp laid across the end of the stump. Usual procedures in such a case would be to cover the end of the stump with a free skin graft or to transfer a flap to it from the thenar eminence. The objection to the latter is that in a 35-year-old man the joints would stiffen in the three weeks that the flap is attached. Perhaps the best way would be to use a cross-finger flap from the dorsum of the long finger and skin graft the donor site. Another possibility would be to raise an immediate pedicle flap from the abdomen and place it over the end of the finger. Such a procedure is usually left for a secondary operation, if it proves to be necessary. If bone is projecting, it should be trimmed off, and, if a joint surface is presenting, it should be denuded of cartilage.

TREATMENT OF PEDUNCULATED POLYPS

To the Editor:—*Two polyps were excised recently from a 53-year-old male. The polyps were attached to the sigmoid flexure by a stalk about 2 in. in length. The microscopic report revealed that the stalk portion of the glandular mucosa is not unusual. A portion of the distal part of the polyp showed hyperchromatism of some of the irregular glandular acini. Heaping up of the glandular epithelium was seen at this portion, with component cells exhibiting moderate variation in size and shape. Mitotic figures are fairly frequent in this area. The diagnosis was malignant adenomatous polyp. At operation the polyp was excised at the base of the stalk. Is any further surgery indicated at present?* *M.D., New York.*

Answer.—Review of the experience at a large cancer center where several thousand pedunculated, adenomatous polyps have been removed showed there has been no instance of lymph node metastases when cancerous changes have been superimposed upon the periphery of the polyp. It would seem, therefore, that the 53-year-old patient having two pedunculated polyps has been adequately treated and that future emphasis should be directed at the detection of other polyps, which are quite likely to develop in other areas of the same lower intestine. Pedunculated carcinomas and sessile polyps, containing foci of adenocarcinoma, on the other hand, have been seen to metastasize to the regional lymph nodes and must be treated radically from the onset as infiltrating carcinoma.

BRANCHIOGENIC CYST

To the Editor:—*What would be the recommended treatment of a healthy 14-year-old girl with a now quiescent congenital cyst (and/or fistula), branchiogenic, in the lateral cervical region, which has twice previously necessitated incision for local abscess formation?* *M.D., California.*

Answer.—A branchiogenic cyst with recurrent fistulous communication is a distinct indication for a complete and adequate excision of the cyst. Incision alone would of course only allow repeated recurrent draining abscess formation, and the actual cyst itself must be removed totally by meticulous and careful surgery.

DIABETIC NEUROPATHY WITH INCONTINENCE

To the Editor:—*What is the treatment for diabetic neuropathy of the legs with incontinence of the bladder and rectum? Are steroids of any value?* *M.D., New Jersey.*

Answer.—The treatment of diabetic neuropathy with incontinence of the sphincters is very unsatisfactory. Some improvement has been noted after intensive treatment with crude liver extracts given intramuscularly (3 cc. daily) and large doses of vitamin B_{12}, of the order of 1,000 mcg. per day. The steroids are probably of no help.

EXERCISE AND THE DIGITALIZED HEART

To the Editor:—*How does exercise affect the rate of the completely digitalized heart?* *M.D., Missouri.*

Answer.—Exercise produces less acceleration of the heart that has been digitalized. This is best seen in auricular fibrillation. The amount of this effect depends on the dose of digitalis. The more complete the digitalization, the less the acceleration of the heart with exercise.